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International Medical Digest

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General Medicine

Treatment of Rheumatoid Arthritis with Deoxycortone and Vitamin C— CURRIE, J. P. AND WILL, GEORGE — *Lancet*, 1: 708 (April 15) 1950.

"Since Lewin and Wassén's original note on the treatment of rheumatoid arthritis with deoxycortone and vitamin C many papers have appeared on this subject. Some observers report results even more dramatic than those with 'Cortisone.' . . . It is regrettable that the favourable reports have often been based on uncontrolled experiments and that subjective improvement alone has sometimes been accepted as evidence of improvement in the joints. Most rheumatologists will agree that one of the difficulties in treating rheumatoid arthritis lies in the accurate assessment of improvement. The clinical application of Kendall's Compound E (cortisone) has been most strictly investigated by Hench and his colleagues due attention being paid to its effect not only on the symptoms of the disease but on the objective signs and range of movements in the affected joints and the erythrocyte sedimentation rate (E.S.R.); these experiments were also satisfactorily controlled.

"This paper records a series of experiments with deoxycortone and vitamin C begun immediately after the publication of Lewin and Wassén's paper and continued until now."

"The 17 patients treated were selected as fulfilling the clinical criteria for a diagnosis of rheumatoid arthritis, and in addition all had: raised E.S.R.; negative Wassermann and Kahn reactions; negative gonococcal flocculation test; normal blood level of uric acid; negative agglutination test for abortus fever.

"All the patients volunteered to come into hospital so that they could be kept under proper surveillance. No patient had less than four injections of the drugs.

"The method of administration used was the popular one—deoxycortone in an oily solution injected intramuscularly, followed within 10 minutes by an intravenous injection of an aqueous solution of vitamin C. The doses were: deoxycortone, 5 mg., and vitamin C, 1 Gm."

The results of treatment in the 17 patients are shown in Table 1. More details are given for specimen cases to illustrate the results of the investigations carried out.

"Great difficulty was experienced in finding an accurate method of joint measurement. The method ultimately adopted was to ring the skin over the maximum diameter with ink and on each subsequent occasion to apply the tape measure to this line." Even so, variations up to 0.5 cm. may arise from experimental error. "Consequently, any change in the joint measurements less than 0.5 cm. is not regarded as significant.

"The E.S.R. and plasma viscosity were measured at constant temperature in a thermostatically controlled water tank."

"Case 1.—A female clerk aged 47, whose symptoms started in 1944. The injections were given on December 19, 1949. The patient said she felt no improvement in the joints, but a sense of mental exhilaration began shortly after the injection and lasted, gradually diminishing in intensity, for about three days. Since she left the wards she has been attending the rheumatic clinic weekly and has been having, by her own request, weekly injections of deoxycortone and vitamin C. She says that her joints are not improved but that she greatly appreciates the 'mental uplift' which lasts for some days after each injection." (Table 2.)

"Case 3.—A housewife aged 43, whose symptoms started in 1943. The injections were given on January 12, 1950. There was no increase in the range of movements. The patient said that the joints

Table 1

Subjective and Objective Changes After Injections of Deoxycortone and Vitamin C in 17 Patients with Rheumatoid Arthritis

Case no. and sex	Subjective improvement	Mental exhilaration	Changes in			
			Joint swelling	E. S. R.	Plasma viscosity	Range of movement
1 F	Definite	Great	Not signif.	Increase	Decrease	None
2 F	None	None	None	Slight increase	Slight decrease	None
3 F	None	Present	None	Great increase	Great decrease	None
4 F	None	None	Not signif.	Decrease	Increase	None
5 F	None	None	None	None	None	None
6 F	Slight, temporary	Present	Not signif.	None	None	None
7 F	None	None	None	Great increase	None	None
8 F	None	None	None	Slight increase	Slight decrease	None
9 M	None	None	None	None	None	None
10 M	None	None	None	Increase	Not signif.	None
11 M	None	None	None	None	None	None
12 F	None	None	None	None	None	None
13 F	None	None	None	None	None	None
14 M	Definite	None	None	None	None	None
15 M	None	None	None	None	None	None
16 F	None	None	None	None	None	None
17 F	None	None	None	None	None	None

Table 2

Joint	Diameters of joints (cm.) before and after injections						
	Before	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
Rt. wrist	15.7	15.7	15.7	15.5	15.5	15.5	15.5
Lt. wrist	14.7	14.6	14.4	14.4	14.4	14.4	14.4
Rt. ankle	24.0	24.0	23.8	23.8	23.7	23.7	23.7
Rt. knee	37.0	37.0	37.0	37.0	37.0	37.2	37.2

Finding	Before	2 hr.	4 hr.	6 hr.
E. S. R. (mm. in 1st hr.)	33	47.0	41.0	42.0
Plasma viscosity (sec.)	38	34.6	35.0	35.0

were not improved but that she felt somewhat exhilarated for two days after the injections. Since leaving the wards she has been attending the rheumatic clinic weekly and has been given, at her own request, weekly injections of deoxycortone and vitamin C." (Table 3.)

"Case 4.—A housewife aged 40, whose symptoms started in 1943. The injections were given on January 12, 1950. There was no increase in the range of movement of the affected joints, and the patient did not feel improved." (Table 4.)

Table 3

Joint	Diameters of joints (cm.) before and after injections						
	Before	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
Rt. wrist	18.0	18.0	18.0	18.0	17.8	18.0	17.8
Lt. wrist	17.2	17.2	17.3	17.4	17.2	17.3	17.2
Rt. ankle	25.4	25.2	25.4	25.5	25.3	25.4	25.2
Lt. ankle	24.2	24.3	24.4	24.4	24.3	24.2	24.4

Finding	Before	2 hr.	4 hr.	6 hr.
E. S. R. (mm. in 1st hr.)	9.0	32.0	38.0	43.0
Plasma viscosity (sec.)	34.8	29.0	31.6	....

Table 4

Joint	Diameters of joints (cm.) before and after injections						
	Before	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.
Rt. wrist	18.5	18.5	18.2	18.2	18.3	18.3	18.3
Lt. wrist	18.5	18.6	18.7	18.6	18.6	18.6	18.6
Rt. ankle	26.5	26.3	26.3	26.3	26.3	26.3	26.3

Finding	Before	2 hr.	4 hr.	6 hr.
E. S. R. (mm. in 1st hr.)	46.0	40.0	46.0	46.0
Plasma viscosity (sec.)	32.0	33.5	32.8	32.4

Table 5

Case no.	After injections of deoxycortone and vitamin C			After injections of saline solution		
	Feb. 21	March 14	March 21	Feb. 28	March 7	March 16
14	Improved	Greatly improved	Improved	Improved	Improved	Improved
1	Improved	Improved	Improved	Improved	Greatly improved	Improved

As will be seen from Table 5, 2 patients reported some symptomatic benefit from the treatment. "At subsequent injections, unknown to them, sterile physiological saline solution was given in place of the deoxycortone and vitamin C." The subjective results are given in this table.

"In rheumatoid arthritis spontaneous remissions are common. These are usually subjective, and are of very variable duration, lasting from a few hours to several months or years. Most patients, indeed, say they have good days and bad days, often associated with changes in the weather.

"The patient's performance is limited not only by the damage to, and the pain in, affected joints but also by his or her

willingness to move the joints." Thus aspirin or any other anodyne (e.g., physeptone) will improve the patient's performance without affecting the disease in other respects. "It must also be common experience to find greater improvement, with any treatment, in the more suggestible and cooperative patients.

"Patients with rheumatoid arthritis may be divided, broadly, into two groups: (1) those who accept their disability as incurable, with the attitude of mind aptly described by the phrase 'What can't be changed must be tholed'; and (2) those who refuse to yield to their affliction and struggle on with their work and recreations in spite of their disability." Symptomatic improvement with any form of treatment is extremely common—at least temporarily—in the second group.

The present investigation has not convinced the writers that deoxycortone and vitamin C, in the recommended doses, are of any value in the treatment of rheumatoid arthritis. The technique the writers have followed does not leave them open to the criticisms directed by Le Vay and Loxton at previous work yielding negative results.

Finally, they feel that in view of the wide differences of opinion regarding the value of this treatment, speculation about the mechanism of its beneficial action is, to say the least, premature.

Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions. A Study in Clinical Physiology — HENCH, PHILIP S., KENDALL, EDWARD C., SLOCUMB, CHARLES H. AND POLLEY, HOWARD F. — *Archives of Internal Medicine*, 85: 545 (April) 1950.

"Patients with rheumatoid arthritis, acute rheumatic fever, certain other diseases with articular complications and certain nonrheumatic diseases have been improved markedly and promptly, but usually temporarily, by intramuscular injections of cortisone or ACTH. Cortisone is the hormone of the adrenal cortex previously known as compound E (17-hydroxy-11-dehydrocorticosterone). ACTH is the pituitary adrenal corticotropic hormone which stimulates responsive adrenal glands to produce cortisone or a cortisone-like steroid such as compound F."

The preliminary results have been reported. Further experiences with these hormones are presented. Because they are still scarce and because experience with them is still limited, this report is presented as a study in clinical physiology and not as a report on clinical therapeutics.

In 1925 the weakness, fatigue and low blood pressure common among patients with rheumatoid arthritis suggested to one of the writers that, in connection with, or in addition to, a supposed factor of infection, secondary metabolic changes were present and that the adrenal glands might somehow be involved in this disease. "But the examination, in 1925, of the adrenal glands of 2 patients with rheumatoid arthritis who died lent no support to the vague suspicion regarding an adrenal factor, and the notion was laid aside for a while.

"In 1929 studies were begun on the amelioration of rheumatoid arthritis by jaundice. It was concluded that, contrary to the general opinion, rheumatoid arthritis was potentially reversible and was 'not necessarily a relentlessly progressive uncontrollable disease for which no really satisfactory and rapid method of control need ever be expected.' " The dominant feature of jaundice suggested that the unknown ameliorating agent, which the writers named "antirheumatic substance X," was a hepatic or biliary constituent. "Hepatic substances and procedures related to jaundice were applied to rheumatoid arthritis without success.

"Between 1931 and 1938 the beneficial effect of pregnancy on rheumatoid arthritis was studied. . . . Was the agent responsible for the relief of rheumatoid arthritis by pregnancy the same as, or closely related to, that operating during jaundice? If so, it could be neither bilirubin nor a unisexual (female) hormone, because jaundiced rheumatoid men obtained the same relief as pregnant rheumatoid women without jaundice. It was then conjectured that the hypothetic substance X was not a disintegration product from damaged liver but probably was a biologic compound specific in nature and function, one which was normal to the human organism and of which, perhaps, the arthritic pa-

tient did not have enough." Since pregnancy alters the concentration of hormones, the writers began to suspect that substance X might be a bisexual steroid hormone. Among substances which came under consideration in 1938 the writers listed whole adrenal cortex extract, then called "cortin," but did not use it until later.

It was noted that pregnancy or jaundice sometimes relieved temporarily such nonrheumatic conditions as hay fever, asthma, sensitivity to egg, migraine and psoriasis. The writers now suspected that if substance X could be identified it would be useful against a number of diseases.

"After five years of work attempting to extract adrenal cortex hormones, Mason, Myers and Kendall isolated compound E in 1935." In lieu of compound E the writers gave Kendall's adrenal cortex extract, "cortin," to 3 patients with rheumatoid arthritis. "The first patient, a girl aged 15 years, was admitted to the Mayo Clinic July 16, 1941. Her polyarthritis was of three years' duration. After she received the extract intravenously (10 cc. twice a day) for four days, certain joints were less swollen and painful; others were still swollen. Similar doses were given for four more days, during which time the earlier improvement diminished. The sedimentation rate fell slightly, from 74 to 60 mm. in one hour. Two other patients so treated also obtained unimpressive results."

With no compound E or other likely adrenal product available the writers produced jaundice with lactophenin in arthritic volunteers. Temporary remissions were induced, but they could not identify the responsible agent.

Enough compound E was not available for clinical testing in human patients until May 1948. "During the next two or three months small amounts were given to a few patients with Addison's disease at three medical centers. Results were satisfactory."

In August 1948, the writers tried to relieve a woman badly crippled with rheumatoid arthritis by means of jaundice induced by lactophenin, but no jaundice developed. They then decided to try compound E if it were available. Their earlier conjecture that substance X might be an adrenal hormone had meanwhile become strengthened by their observations that rheumatoid arthritis was often temporarily relieved by seemingly diverse agents (foreign protein reactions, starvation, various surgical operations and even anesthesia without surgery), some of which were capable of stimulating the adrenal cortices.

"Cortisone or the pituitary adrenal corticotropic hormone (ACTH) has been given to 23 patients with severe rheumatoid arthritis, to 8 patients with acute rheumatic fever, to 6 patients with severe disseminated lupus erythematous with or without associated polyarthritis, to 2 patients with tuberculous arthritis, to 1 patient with severe psoriasis and psoriatic arthritis, to 1 patient with primary osteoarthritis and to 1 patient with polyarthritis associated with chronic ulcerative colitis.

"Cortisone, given to 21 patients with severe or moderately severe rheumatoid arthritis, produced a very marked effect in 12, a marked effect in 8 and a moderate effect in 1. Cortisone was administered, in some cases continuously; that is, daily for periods varying from 8 to 187 days. It was given more or less continuously to 2 patients for a total of 215 and 218 days respectively. Daily doses varied from 25 to 300 mg. but were usually 100 mg. When patients received more than one course, they responded to each course in much the same manner.

"The pituitary adrenal corticotropic hormone, ACTH, which stimulates responsive adrenal glands to make their own cortisone or a cortisone-like substance, such as compound F, was given daily to 6 patients, with severe or moderately severe rheumatoid arthritis for periods varying from 11 to 87 days. The antirheumatic effect was very marked in 4 cases and marked in 2 cases. The daily doses varied from 45 to 140 mg. but were usually 100 mg.

"Most of the symptoms of rheumatoid arthritis responded promptly to cortisone or to ACTH in a characteristic pattern: reduction of stiffness first, then of pain on motion and then of tenderness and swelling." During the use of either hormone some patients became practically symptom free but others still had minor degrees of rheumatic activity.

"Miscellaneous clinical results from cortisone or ACTH included reduction of fever

when present, improved nutrition with increased appetite and weight, frequent development of a sense of well-being or 'euphoria,' reduction or disappearance of several flexion contractures, and reduction in size of subcutaneous rheumatoid nodules and lymph nodes.

"Sedimentation rates during the use of cortisone became normal in 15 cases, became almost normal in 3 and were reduced but not to normal in 3 cases. From ACTH, sedimentation rates became normal in all 6 cases. Rates of reduction were usually fairly rapid, occasionally tardy. Once reduced, the sedimentation rates in some cases remained normal as long as adequate doses of the hormones were given; in other cases they varied in the neighborhood of near normal values and in a few cases rose again.

"Concentrations of hemoglobin and erythrocyte counts increased fairly rapidly in several cases. Abnormally increased serum globulin concentrations were reduced, and albumin-globulin ratios became more nearly normal.

"A variety of metabolic and other biochemical effects were studied. In general they bore a quantitative relation to the doses of cortisone or ACTH used and to the duration of administration. There was a general tendency for an initial retention and later a liberation of salt and water and reduction of serum potassium, but in only 1 case was the last severe. Cortisone in doses of 100 mg. daily usually induced minimal or no alterations in plasma electrolytes or in balance for sodium, potassium, chlorides or nitrogen; but daily doses of 200 mg. of cortisone or of 100 mg. of ACTH sometimes produced a negative nitrogen balance and a transient hypochloremic hypopotassemic alkalosis. When present, the latter was often mild and apparently nonproductive of symptoms; occasionally it was marked and appeared to be correlative to certain symptomatic side effects.

"No marked impairment of carbohydrate tolerance occurred among the 23 rheumatoid patients given cortisone or ACTH, although administration was prolonged in several cases. Fasting blood sugar levels remained normal: No significant glycosuria developed. Glucose tolerance tests were performed during the use of cortisone in 9 patients: Results were normal in 5 and abnormal in 4." These hormones when given in the doses usually employed in the writers' cases do not markedly reduce carbohydrate tolerance in rheumatoid patients who do not have latent or frank diabetes. "But in any patient with latent or frank diabetes these hormones should be expected to produce transient reduction of carbohydrate tolerance.

"Articular biopsies, made in several cases before and after receipt of various amounts of cortisone or ACTH, revealed that definite, sometimes marked, reduction of synovial and subsynovial inflammation resulted from use of the hormones.

"When cortisone or ACTH was withdrawn, symptoms and signs of rheumatic activity usually returned, in most cases quickly. But in a few cases symptoms remained in abeyance for from two weeks to a few months, and in 2 cases the hormone-induced remissions have persisted for 10 and 12 months respectively.

"The prolonged use of either of these hormones may produce side effects of different types. Of the 23 rheumatoid patients no significant side effects developed among 9; they received cortisone or ACTH for a total of about three weeks to four and one-half months. Mild side effects, such as mild acne, mild hirsutism, rounding of the face or mild irritability, developed among 8 patients given continuously or almost continuously one of the hormones for from 11 days to 7 months. Moderate side effects developed in 2 patients given cortisone or ACTH for a total of 95 and 101 days. More disturbing or 'marked' side effects developed in 4 patients during the administration of cortisone or ACTH for from 12 to 187 days.

"Most patients tolerated well 100 mg. of cortisone or a corresponding amount of ACTH daily for at least a month or two. When side effects occurred, they usually (but not always) developed in patients who received one or the other hormone continuously for a relatively long time or 'large doses' for a shorter time. Although the development and nature of the side effects depended largely on dosage and duration of administration of the hormones, individual tolerances played a role. Males tolerated greater doses and longer admin-

istration than did females, especially adolescent or menopausal females.

"A few side effects were related to current 'impurities' in ACTH, not to ACTH itself. The hormonal side effects concerned shifts of fluid and electrolyte balance and characteristic changes in certain bodily tissues and functions. The commoner side effects consisted of certain transient paresthesias or somatic symptoms resembling those considered 'functional' and may have resulted from transient vasomotor changes or transient alterations in tissue fluids and electrolytes. Other effects of hypercortisonism resembled those seen in Cushing's syndrome, such as rounded face (which occurred in 7 patients), amenorrhea (which occurred in 1 rheumatoid patient), mild hirsutism (which occurred in 7 patients), mild acne (which occurred in 2 patients) or striae (which developed in 1 patient). Minor alterations of psyche (euphoria, mild nervousness) often occurred. In 1 patient who received cortisone continuously for 187 days depression clearly developed after about five months and at one time became fairly severe.

"A few side effects became evident not during but after the use of the hormones; chief of these withdrawal effects was a sense of exhaustion and weakness, which usually disappeared after four weeks or so. Temporary reduction of adrenal cortex function was considered as a possible cause.

"These side effects have, to date, been transient and reversible.

"No significant changes in blood pressure occurred in any of the rheumatoid patients. But in a patient with severe lupus erythematosus disseminatus with renal involvement, the blood pressure increased notably when the daily doses of cortisone were increased to 150 mg. Later, when the dosage was decreased, the blood pressure fell again.

"The antirheumatic and certain other effects from ACTH were essentially the same as those from cortisone, but 100 mg. of ACTH apparently stimulates the production of considerably more than 100 mg. of cortisone, perhaps 200 mg. or even more. Therefore, some of the effects, especially the side effects, from 100 mg. of ACTH were somewhat prompter and more marked than those from 100 mg. of cortisone. ACTH is, of course, effective only in patients with responsive adrenal glands. The adrenal glands of most, but not all, persons with rheumatoid arthritis are responsive. A patient with rheumatoid arthritis or another condition affected by these hormones will, if his adrenal glands are unresponsive, not benefit from ACTH but may respond to cortisone.

"Compound A (11-dehydrocorticosterone) given to 3 patients had no effect on joints or on sedimentation rates."

Compound F (17-hydroxycorticosterone) decreased rheumatic symptoms and the sedimentation rate in 1 patient. This and other data suggest that cortisone and compound F have essentially the same antirheumatic activity. Compound F and not compound E (cortisone) was recovered from the urines of the writers' patients given ACTH.

"Acute manifestations of rheumatic fever were generally abolished promptly by cortisone or ACTH. No evidence of new, or increased old, rheumatic carditis was observed within the following 8 to 10 months."

"A patient with severe disseminated lupus erythematosus was markedly benefited by cortisone. Certain systemic manifestations regressed as well as associated arthritis.

"A patient with severe psoriasis with psoriatic arthritis responded to cortisone and to ACTH.

"Cortisone affected favorably certain hyperergic responses in 2 cases of tuberculous arthritis and reduced symptoms and sedimentation rates but did not produce bacteriologic or pathologic remissions.

"An osteoarthritic joint of 1 patient became symptomless as a result of cortisone given for his leukemia. The articular and intestinal symptoms of chronic ulcerative colitis were notably affected by cortisone in 1 case."

"Coincidentally with the effect of cortisone on rheumatoid arthritis, symptoms of hay fever decreased in 2 cases and of bronchiectasis in 1 case; a chronic neurodermatitis cleared in 1."

"The observations of others on the effects of cortisone and ACTH on certain articular conditions, especially gouty arthritis, were reviewed. Patients with mild

rheumatoid arthritis responded to 50 mg. of cortisone daily.

"Several articular and other inflammatory reactions have been temporarily relieved when adequate amounts of cortisone were provided."

Since in 74 per cent of the 23 rheumatoid patients no troublesome side effects developed while one of the hormones was being given for periods varying from two weeks to a few months, it would appear that side effects may not present an important problem in the investigative management of most cases of acute rheumatic fever, acute gouty arthritis, acute crises of disseminated lupus erythematosus and other conditions, such as seasonal allergies, in which relatively short term administration may suffice.

"For those conditions which would seem now to require long-continued use, methods should be found to prevent, control or combat if possible undesirable side effects. . . . The combined use of estrone and cortisone appeared to prevent most of the annoying symptomatic side effects which developed in 1 menopausal patient from cortisone alone; nitrogen and potassium deficits, if they occur, can probably be controlled by special diets and the administration of potassium. Testosterone minimized the nitrogen deficit in 1 case. But the best guarantee against side effects now is to use, possibly intermittently, the smallest effective daily and total dose.

"Daily doses of 200 mg. of cortisone or 100 mg. of ACTH should be considered 'high,' ones which may be well tolerated by most patients for fairly short periods only and from which side effects may usually be expected within a relatively short time. Such doses should be regarded as suitable only for short term use or for emergencies, such as acute crises of lupus erythematosus or acute rheumatic fever. Continued tolerance for daily doses of 100 mg. of cortisone or for comparable amounts of ACTH (50± mg.) is much greater. But whenever possible, or as soon as possible, the smallest effective doses should be used.

"The optimal dosage and method of administration of cortisone and ACTH remain to be determined and may not be established without more information about the physiology and metabolism of ACTH, cortisone and compound F. A few data suggest that the intermittent administration of either hormone, or interrupted alternating courses thereof, may provide a more physiologic response than the use of either hormone given continuously to the limits of individual tolerance. In the presence of functioning adrenal glands, one must learn how to cooperate with them rather than to dominate them or to try to take over their functions."

The use of these hormones should be considered an investigative procedure, not a treatment. "The value of these hormones at present is that their use will permit the study of certain disease mechanisms more carefully than heretofore." One can now repeatedly produce controlled remissions of several diseases, to be followed by more or less controlled relapses, both of which processes can be studied intensively by a variety of clinical, biochemical and immunologic methods. "It is hoped and believed that such studies will in time lead to an improved and practical method of treatment. But this present study is to be regarded, not as a report on clinical therapy, but as an investigation in clinical physiology."

Deoxycortone Acetate and Ascorbic Acid in Ankylosing Spondylitis in Correspondence from Jerusalem — ZONDEK, HERMANN — *Lancet*, 1: 517 (March 18) 1950.

The writer has used the method reported by Lewin and Wassén in cases of acute and chronic rheumatoid arthritis with the varying results recorded by subsequent investigators.

"Most pronounced and surprising was the beneficial effect of this treatment in 2 cases of Bechterew's disease. The duration of the illnesses was 12 and 13 years. Radiologically both patients were shown to have severe ankylosing changes of the vertebral column.

"About 15 minutes after the first injection, 1 patient was able to move the head in all directions and to bend his back, which had been completely rigid; and during the next two hours mobility increased still further. After the second injection he was able to lie down quickly and to get up from the floor, to take off and put on his clothes (which previously had been

possible only with the help of others), to lift and rotate his legs and arms. The effect of the second injection lasted for 48 hours. The patient, who was an ardent tennis player before the onset of the disease, felt as though he 'might start playing again.'

"The second patient, who complained particularly of complete stiffness of the neck, responded less dramatically than the first. Yet 15 minutes after the first injection he turned his head about 25° to each side, and after approximately one hour he managed to move it slightly forwards and backwards. After another half hour the mobility of the thoracic and lumbar spine also increased somewhat."

The writer recalled having treated arthritic changes by ovarian transplants about 25 years ago. In some of his cases transplantation of a juvenile ovary led to surprisingly good results. Accordingly, the writer administered oestrogenic hormone (50,000 units) and five minutes later vitamin C (1 Gm.) intravenously to some female patients suffering from rheumatoid arthritis; there was either no response or at best a slight response. "Progesterone (5 mg.) administered in the same way, however, produced in 3 cases the same favourable results as deoxycortone; in 1 case progesterone proved even more effective than deoxycortone."

Observations on Late Post-Transfusional Jaundice — Romero Alvarez, Augusto M.—*Anais paulistas de medicina e cirurgia*, 59: 201 (February) 1950.

Jaundice from homologous serum has not been observed frequently as many patients return early to distant places, but the low incidence is also linked to the fact that plasma pooled from many donors has been used very little since attention has been called to this type of jaundice. It is known that 1 part of plasma can contaminate 500 times its volume, and avoidance of pooling is of greater advantage in prevention of jaundice than ultraviolet irradiation. However, completely unpooled plasma carries a greater risk from agglutinins if the blood group cannot be determined because of emergency conditions, and the author therefore uses mixtures of plasma from 8 donors; such mixtures carry the potential risk of jaundice for 4 recipients with the commonly used dosages.

The author's material includes 32 cases of serum jaundice; only 1 of them was severe and caused the patient's death. The incubation period ranged between 39 and 120 days and the syndrome started with general weakness, slight fever, abdominal pain, and anorexia with or without nausea; after two to five days acute catarrhal jaundice supervened. The jaundice persisted for three to four weeks.

Among 300 patients seen six months after having received transfusions 9 suffered from jaundice and 7 showed dyspeptic manifestations which may be interpreted as anicteric forms of serum jaundice. Infectious jaundice was carefully ruled out in all cases. One man aged 73, received six plasma transfusions and three blood transfusions at the occasion of a colectomy for cancer of the transverse colon; he developed progressive jaundice with a highly positive Hanger reaction, and five days after onset acute liver insufficiency supervened and proved fatal within 24 hours. Autopsy revealed subacute hepatitis with destruction of the liver parenchyma. The liver was reduced in size, of increased consistency and showed abundant blood on section; the centrilobular veins were well marked and around them the parenchyma was a dark yellowish color, with alternate friable and firm areas. The microscopic picture was that of a highly exudative subacute hepatitis particularly at the level of the portal spaces in which an exudation of round and polynuclear cells predominated. In the center of the lobules the liver cells had almost completely disappeared and were replaced by a sclerotic tissue; there was discrete hyperplasia of the perilobular tissue, and fatty metamorphosis. The microscopic findings confirmed the hypothesis of some authors concerning the effect of anoxia by congestion on the liver cells. The autopsy also showed renal, splenic and pancreatic arteriosclerosis; the surgical field was well peritonized.

In 1946, one lot of plasma, prepared from 20 donors and totalling 4,200 cc., was used on 11 patients. Of these, 3 succumbed to their respective diseases; namely, trauma, gangrenous appendicitis and neoplasm of the pancreas, 3 developed no complications and 4 developed jaundice 72

to 79 days after the transfusion, while the eleventh patient was lost sight of and could not be contacted. Thus this lot proved highly icterogenic. Interestingly, all donors could be contacted, and none of them suffered from jaundice or dyspeptic manifestations; no such manifestations were encountered in the family of any of them. A healthy carrier of the virus must have been dealt with.

The histologic examination in the fatal case showed the general structure of the liver to be well preserved, and the lobular outlines with central vein and peripheral Kiernan's spaces could more or less be well distinguished. The cellular lesions predominated in the central zone of the lobules where only necrotic residue of the liver trabeculae persisted and where instead of the trabeculae congested sinusoids, hemorrhages and macrophages were encountered. Due to this necrosis, the distance between the central vein and portal space was diminished, and the lobules were decreased in size. In the rest of the lobule a considerable number of liver cells were hypertrophied and showed a marked increase of the cytoplasm and particularly the nucleus which was hyperchromatic and often double. Karyokineses were absent. All sinusoids were congested and Kupffer's cells showed a tendency to assume a round shape and seemed increased in numbers. The Kiernan spaces contained an abundant cellular inflammatory exudation, with predominance of round cells with a scanty cytoplasm and a dense nucleus; typical histiocytes and neutrophilic polynuclears also were encountered, and only occasionally eosinophils. Between the inflammatory elements a more or less well developed fibroblastic network could be perceived. The bile ducts were increased in numbers, up to five or six being encountered in Kiernan's space. Some lobules were more intensely involved than others. High magnification showed dilatation of the intralobular biliary capillaries which were filled with bile. The normal or hypertrophic liver cells showed cytoplasmatic hemosiderin and lipofuscin granulations. The Sudan stain showed fat in fine and medium-sized droplets, both in the liver cells and the macrophages, particularly those in the center of the lobules. The Río-Hortega method demonstrated an apparent, and real although discrete increase of the reticulin in the center of the lobules, and also an increase of the collagenic fibers, and to a lesser extent, of the reticular fibers in Kiernan's spaces. Thus the histologic diagnosis was frank hepatitis with intense centrolobular necrosis, marked hypertrophy of the rest of the liver cells and cellular inflammatory exudation, particularly abundant in the Kiernan spaces.

Present Status of the Antihistaminic Drugs in the Common Cold — EDITORIAL — *New England Journal of Medicine*, 242: 596 (April 13) 1950.

"In response to many requests for a considered opinion concerning the validity of the extraordinary claims made by the aggressive promoters of the antihistaminic drugs, which were released by the Food and Drug Administration for over-the-counter sale, the Council on Pharmacy and Chemistry of the American Medical Association has published a critical review of the status of the agents in the prophylaxis and treatment of the common cold. In this review the Council analyzed the details of the published reports for the accuracy of the diagnosis of the common cold, the adequacy of the controls used in assessing the results and the statistical significance of the reported results.

"The reports analyzed included 2,357 patients with the common cold, more than half of them studied by a single observer. From these reports the Council concluded that the diagnostic methods employed did not conclusively demonstrate that the condition treated was actually the common cold. Over half the cases were investigated in studies with inadequate controls or without controls, and the interpretations of the results obtained are open to question. The results of the only published prophylactic study are considered to be suggestive in that the figures as recorded are statistically significant, but these results require confirmation because the series is small and the findings are contrary to the experience of allergists.

"The Council pointed out many flaws in the experimental design of these investigations that introduce serious doubts of the validity of the results. Furthermore, the side effects from the antihistaminic drugs

that have been encountered by all observers are quite significant in frequency and may be quite serious under certain circumstances or in some cases. These have not been adequately emphasized in the reports, and they have been either minimized, almost completely ignored or denied by the lay promoters in their advertising campaigns.

"The evidence so far presented, in the considered opinion of the Council, should be properly classified as the honest opinion of the investigators but not as fact. The Council concedes that the antihistaminic agents apparently produce considerable subjective relief owing to inhibition of nasal discharge, but it states that similar results may be obtained by the use of ephedrine or atropine.

"The Council also took this opportunity to make certain suggestions for studies that would lead to the solution of the fundamental problems of the pathogenesis of the common cold and would resolve the controversial claims concerning the effectiveness of the antihistaminic drugs in its prevention and treatment. For example, further work is indicated to delineate clearly the influence of histamine in the pathogenesis of the common cold, since some of its early symptoms have been reproduced by spraying of a dilute histamine solution on the nasal mucous membrane. This is obviously a reasonable and pertinent suggestion.

"The Council, however, goes on to suggest an outline of an investigation to obtain more conclusive clinical data for evaluating the antihistaminic agents. For this purpose they propose that a supply of an 'unquestionable causative agent of the common cold' be obtained by a technic similar to that used by the workers of the National Institutes of Health in isolating their common cold virus. 'A large group of normal volunteers in whom allergy has been eliminated' should then be divided into suitable treated and control groups for prophylactic and curative studies with various dosages and time schedules. Further details are suggested, and the Council report concludes by stating that 'until a scientifically acceptable study is performed, the true effectiveness of the antihistaminic drugs in the control of the common cold cannot be evaluated.'

"Although it is difficult to take exception to this concluding statement, it seems equally obvious that the type of study proposed by the Council is far from realistic. Several groups of workers like those at the National Institutes of Health and the Commission on Acute Respiratory Diseases in this country and at the Harvard Red Cross Hospital in England have made extensive and elaborate efforts to obtain a solution of the simple problem of the isolation, identification and maintenance of viruses from patients with the common cold and other simple respiratory infections. An analysis of the details involved in carrying out these studies would almost be enough to discourage any undertaking of the type suggested by the Council. Furthermore, it is doubtful whether any medical research unit now in operation, including the ones just mentioned, has or could obtain the facilities and funds required to carry to a logical conclusion the investigation suggested by the Council.

"It might be suggested, of course, that the chief source of support for such a huge and expensive project might be derived from the enormous profits being realized from the tremendous sales of these antihistaminics. It is hardly to be expected, however, that those who are exploiting these drugs for personal profit have sufficient interest in the truth of their claims or in the welfare of their customers to stake a sizable share of their income in an attempt to arrive at a truth that might possibly disprove these claims and would remove much of the source of these newly acquired profits. And even if the funds were made available, it may be seriously doubted if such an investigation could be carried out successfully in the present state of knowledge of the viruses of the common cold and of the technics required for controlling the studies with such agents.

"A more realistic approach to the immediate problem of the evaluation of the claims concerning the efficacy of the antihistaminic agents against the common cold must take into account the difficulties in diagnosis and utilize the best available clinical criteria. Perhaps it might be more reasonable to suggest a large scale and carefully controlled study such as that conducted by the Medical Research Council of Great Britain following the flurry of

excitement caused by the claims concerning the effectiveness of the antibiotic 'patulin' in the common cold. This large scale study might be supplemented by a number of small and carefully controlled studies on the role of allergy and histamine in various upper respiratory tract syndromes and their possible relation to the common cold. Meanwhile, many studies under way have been planned by different groups of workers from various points of view. The results of these studies are awaited with considerable interest, for, although they may not come up with conclusive answers to the immediate problem or satisfy the rigid criteria of the Council, they may help to evaluate or delineate the role of the antihistaminic drugs in various affections of the upper respiratory tract."

The "Rh" Problem. A Discussion of Pertinent Questions — HAMILTON, EUGENE G. AND BROCKLAND, MARY ELIZABETH — *Journal of Missouri State Medical Association*, 47: 185 (March) 1950.

The discovery of the "Rh factor" and the proof of its place in the etiology of the syndromes assembled under the heading of "erythroblastosis fetalis" has led to a welter of articles on all phases of the subject. "In spite of all the work done in this field, the unanswered questions predominate. In fact, one is more acutely aware of his ignorance and confusion now than before these discoveries were made.

"The laboratory tests developed to study the Rh problem have themselves confused the issue for the profession in general. The purpose of this presentation is to set forth the uses and limitations of such tests and the fundamental concepts by which each is interpreted. There is urgent need for more intelligent study of all cases of isoimmunization if remedial measures are ever to be discovered and evaluated.

"1. What Does a Laboratory Report of 'Rh Positive' or 'Rh Negative' Mean?—The use of the term 'Rh' is confusing and, for clarity, as far as the printed page is concerned, it is better avoided. There are six different antigens in this category that may occur in human erythrocytes. These have been designated as C (or Rh′), D (or Rh_0), E (or Rh″), c (or Hr′), d (or Hr_0) and e (or Hr″). The English system employing C, D, E for the 'Rh' antigens and c, d, e for the 'Hr' antigens is . . . . easier to visualize and comprehend, continuing as it does from the A-B designation of the major blood groups.

"Depending upon hereditary factors, there may be almost any combination of the antigens C, D, E, and c, d, e.

"The specificity of the typing serums used varies in different laboratories. Some use serum which will agglutinate erythrocytes containing D (Rh_0), the so-called 83 per cent serum. Others use CD (Rh_0') serum, or the so-called 87 per cent serum which will cause agglutination of erythrocytes containing C or D or both. In interpreting results it is important to know which serum the laboratory uses. In fact, the laboratory report should show which antigen or antigens they have found present when they report a 'positive.' An 'Rh-negative' report means that the particular antigen tested for in the laboratory was absent.

"2. Why Is the Same Patient Sometimes Reported 'Positive' by One Laboratory and 'Negative' by Another?—Weak typing serums may be a factor. However, as can be derived from the discussion of question 1, such a report is possible with potent serums also. A patient whose erythrocytes contain C but not D would be reported 'negative' by the laboratory using anti-D (Rh_0) serum, and 'positive' by the one using anti-CD (Rh_0') serum.

"3. Can an 'Rh-Positive' Woman Have an Erythroblastotic Infant?—Yes. It should be understood that, potentially, one can be immunized by any of the antigens not contained in one's red cells. Therefore, a woman whose cells contain C, but not D or E (and who is reported 'Rh-positive' by a laboratory employing anti-CD serum) may produce antibodies to D and E or E. If she were sensitized to either or both D and E, and the antigens were in the red cells of her fetus, she could give birth to an erythroblastotic child."

The same outcome also may be the result of an ABO incompatibility in an "Rh-positive" woman.

"Similarly, a woman whose cells contain no c antigen can be sensitized to this factor by a fetus having it. Such cases sometimes are designated 'Hr' incompatibilities,

and have been reported but they are rare because c is a relatively weak antigen.

"4. What Is the Meaning of 'Heterozygous' and 'Homozygous Rh-Positive'?—These terms may be said to indicate whether a person is 'whole-blooded' or 'half-blooded' as far as a given 'Rh' antigen is concerned. In an effort to determine whether a sensitized woman could possibly conceive an 'Rh-negative' child sired by the husband, the genotype of the husband is checked and, if possible, his parents. For example, if both the paternal parents are homozygous for D, then the father is homozygous. If the parents are heterozygous for D, the potential father may or may not be heterozygous.

"The genotype of any person may be guessed from the reaction to the available antiserums for C, D, E and c. According to the computations in table 1 . . . . one can evaluate the accuracy of such a report.

"5. What Tests Give an Indication of the Presence of 'Anti-Rh' Antibodies?—The test for 'saline agglutinins' determines the presence of agglutinating or 'complete' antibodies. In this test the patient's serum is added to cells suspended in saline solution. But if 'blocking' antibodies are present any saline agglutinins may be masked.

"The test for 'blocking' antibodies is done when the test for saline agglutinins is negative. In the more severe types of sensitization, or isoimmunization, 'blocking' antibodies are present. They so coat the erythrocytes that when suspended in saline solution in the presence of potent anti-Rh serum, agglutination is prevented."

Table 1. The Errors Involved When the Genotypes Are Guessed from the Reactions of Anti-C, Anti-D, Anti-E and Anti-c.

Reaction of blood with: Anti-C	Anti-D	Anti-E	Anti-c	First guess	Reasonably common alternatives	Approximate errors in: (1) Unselected persons	(2) Fathers of children with hemolytic disease.
+	+	−	+	CDe/cde (32.7%)	CDe/cDe (2.2%)	6%	21%
+	+	−	−	CDe/CDe (17.7%)	CDe/Cde (0.8%)	4%	1%
−	+	+	+	cDE/cde (11%)	cDE/cDE & cDE/cDe (2.7%)	20%	49%
+	+	+	+	CDe/cDE (11.9%)	CDe/cdE & cDE/Cde (1.3%)	10%	3%
				In the following 7 combinations representing the most common genotype in each reaction group the errors are very small.			
−	−	−	+	cde/cde			
−	+	−	+	cDe/cde			
−	−	+	+	cdE/cde			
+	−	−	+	Cde/cde			
+	+	+	−	CDe/CDE			
+	−	+	+	cdE/Cde			
+	−	−	−	Cde/Cde			
Percentage frequency of positive reactions given by these serums							
68	83	29	81				

The "conglutination test" is sensitive to blocking antibodies, and by serial dilutions (in a protein medium) of the serum being tested an attempt is made to arrive at a "titer."

"The Diamond and Abelson slide test is a qualitative determination for isoimmunization, positive in the presence of blocking antibodies.

"The Coombs, or antihuman globulin, test is based on the fact that serum from an animal (sheep), sensitized to human globulin, will cause agglutination of red cells coated with anti-Rh antibodies. The test picks up any kind of Rh antibodies. It is nonspecific since other globulins on erythrocytes may give a positive reaction. However, a positive finding using the cells of a newborn infant may be assumed to be due to Rh antibodies, particularly when the parental types fit the picture. In rare instances group K or S may be involved.

"The 'direct' Coombs test is the one just described. The 'indirect' Coombs test is used to examine the serums of patients suspected of having Rh antibodies. In this instance type O Rh-positive cells are incubated with the patient's serum to allow them to become coated with the antibodies. These cells are then tested, after proper washing, with the antihuman globulin serum as in the direct test.

"Modifications of this procedure, using serial dilutions of the serum to be tested, have been employed for a quantitative test in an effort to arrive at a 'titer.' This test is probably more sensitive than other antibody determinations.

"6. Are There Different Types of Antibodies, Against D for Example?—Yes. (1) There are agglutinating antibodies, the so-called complete antibodies, as mentioned in question 5. Some maintain these do not cross the placental barrier because of their large molecular size. (2) The 'blocking' antibodies also are discussed in question 5. These pass the placental barrier and are credited with producing the bulk of the fetal damage. (3) Still more incomplete antibodies, the so-called 'cryptagglutinoids,' are most easily demonstrated by the Coombs test. They cause neither blocking nor agglutination in vitro, and their clinical import has not been established.

"The agglutinating and blocking antibodies, at least, are specific for each antigen. It is thus possible for a mother to carry perhaps four to nine different types and specificities of antibodies, particularly if the sensitizing bloods were not all of the same genotype.

"It becomes obvious, therefore, that there will be considerable variation in the 'titers' as reported by a laboratory using the conglutination method depending on the relative strength and specificity of the individual antibodies together with the genotype (or genotypes) of the test cells.

"Likewise, since the genotype of the baby must remain unknown until birth, the determined antibody level may or may not be a measure of the antagonism against the fetal cells.

"Consequently, there are many pitfalls to using the titer in prognosticating the degree of fetal involvement.

"7. Does a Positive Maternal Antibody Titer Mean the Baby Will Be Erythroblastotic?—Not necessarily. The antibodies may persist from a previous pregnancy or transfusion. If the first titer is taken in the last trimester of pregnancy, one has no way of determining whether or not the antibodies were produced in that pregnancy. Even if the previous child is Rh-positive and did not have erythroblastosis, the antibodies could still persist from that pregnancy. This is true because the titer may have risen too late in that pregnancy to have affected the baby, or the antibodies may have been produced in the puerperium. The same holds true for a primigravida previously transfused with Rh incompatible blood.

"If the fetus is Rh-negative (cde/cde) in such instances, or if the cells do not contain the factors specific for the maternal antibodies, the baby will not have erythroblastosis. For example, if the antibodies are against D and E, and the baby has only C, it will not be involved.

"8. Does a Negative Maternal Antibody Titer Rule Out Erythroblastosis in the Newborn?—In general, yes; particularly if the Rh antibody determination is accurate and is found negative a few days prior to or at the time of labor. However, major group incompatibilities occasionally produce erythroblastotic babies. For example, a type O Rh-positive mother carrying an A, B or AB fetus (Rh-positive) may deliver an erythroblastotic baby.

Other incompatibilities even more rarely may be responsible; as for example, K, Celiano or S.

"9. How Accurate Are Rh Antibody 'Titers'?—Their accuracy can in no way approach those of chemical tests such as blood sugar, or nonprotein nitrogen. The end points depend upon the presence or absence of agglutination, and this is not a clearcut phenomenon. Some workers can 'see' agglutination where others do not. Much, therefore, depends upon the judgment and training of the technician, the concentration of the suspended cells and the medium in which they are suspended. In general higher 'titers' have been found when normal adult human serum was used than when 20 per cent bovine albumin was added.

"The specificity of the cells used in the test with relation to that of the antibodies in the serum being tested is also an important factor. For example, cells of genotype cDE/cde when used to test the serum of a patient with antibodies against C and D would yield a lower 'titer' than if tested with cells of genotype CDe/CDe.

"Ordinarily, if the test is properly performed in the same laboratory, under identical conditions, by the same technician readings should not vary more than one tube in serial dilutions. However, this might appear to be quite a variation in higher titers where one tube would be the difference between 1:512 and 1:1,024. Between different laboratories much greater disparity will be found to exist, especially if proper controls are not set up. For this reason it is difficult to evaluate case reports from all over the country.

"10. Does a Rising Titer Mean the Woman Carries an Rh-Positive Baby?—No. Mollison states that, 'If the titer increases around twentyfold or more, it can be considered extremely likely the infant in utero is Rh-positive—.'" One of the writers' patients with a history of 3 erythroblastotic babies, the last 2 being fatally involved, presented herself two and one-half months pregnant with a conglutination titer of 1:64. "By the time she reached term the titer was varying between 1:1,024 and 1:2,048. Levine's laboratory reported 1:1,024. She delivered a normal Rh-negative infant at term."

"11. Does a Fairly Stationary Titer Throughout Pregnancy Mean the Baby Will Be Rh-Negative?—No. Some patients seem to reach a certain level beyond which they do not go and this may be only 1:32 or 1:64. However, such a titer is high enough to produce a fetal hydrops, or fatally involved nonhydropic erythroblastotic baby. The duration of such a titer can be more important than its height.

"12. Can One Predict the Probable Degree of Fetal Involvement from Study of the Maternal Titers?—No. Not even all Rh-positive babies are involved to the same degree by a given titer. In general, the higher the titer and the longer it exists throughout pregnancy, the more severe the degree of involvement. Attempts have been made to correlate these factors with a view toward predicting the fetal condition. But for an isolated case they are unreliable, and exceptions to the rule are not rare. More thoroughly followed cases must be reported before the picture can be clarified. Such studies must include the titers of the specific antibodies along with the genotype of the baby."

13. Is It Possible at Present to Get Complete Blood Studies in Commercial Laboratories in Missouri?—The writers know of no such laboratories. "Even if these studies could be made, the number of tests required to follow a case would make the cost prohibitive in most instances. One or more central laboratories, subsidized by some means and staffed by specially trained personnel, would be required for proper studies. Ideally, all cases checked by the central laboratory should be followed according to an established schedule which would result in worth while clinical observations.

"14. With the Facilities Now Generally Available What Tests Are Suggested?—A suggested minimum would include:

"1. Rh typing of all obstetric patients.

"2. Typing of husbands of women found to be Rh-negative.

"3. Titers on Rh-negative primigravidas with Rh-positive husbands at about eight months' gestation. (It is assumed that these give no history of possible isoimmunization by transfusion, plasma, or intramuscular blood.)

"4. In multiparas obtain a titer as early as possible and repeat about twice during

the first six months, and monthly thereafter, the last being as near term as possible. In general, if the baby can be delivered three weeks or less from term and is exposed to antibody titers over 1:4 for less than 6 weeks, it will be mildly involved if at all.

"5. In primigravidas, with a history of possible previous sensitization, the same program should be followed.

"Such studies will enable one to be prepared, when necessary, for intensive treatment of the baby. They do not constitute a complete work-up, and departures from the predicted will occur frequently.

"15. What Can Be Done to Prevent Isoimmunization?—The most important single factor is the complete typing of female recipients from birth to the menopause, as well as their donors.

"In addition to the necessary checks for ABO incompatibility, CDE compatibility also should be insisted upon whenever the time factor does not preclude it.

"For example: A recipient, genotype Cde/cde is typed with anti-CD (RH_0') serum and found to be 'Rh-positive.' She is given Rh-positive blood that happens to be genotype cDE/cDE. She becomes sensitized to D and E. She later conceives a baby whose cells contain D and E or E and loses it with erythroblastosis. Or she is given cDE/cDE blood later and suffers a fatal reaction.

"Another example: A recipient, genotype cde/cde (Rh-negative) is given 'Rh-negative' blood tested only with anti-D (Rh_0) serum. The donor turns out to have C and E or E and the recipient is sensitized. If a child is later conceived whose red cells contain one or both of these factors it might be involved fatally.

"Similar sensitizations can occur with the cde antigens, or with the Cellano factor, but their rarity justifies disregarding them.

"16. Is There Any Method at Present Available for Treating Mothers During Pregnancy to Reduce the Severity of the Disease in the Baby?—No feasible method has as yet been established.

"17. What of Cesarean Section to Increase Fetal Salvage?—The use of cesarean section has been largely discredited. If the woman has lost several babies from erythroblastosis and in the present pregnancy carries one of identical genotype, the outlook for the baby is not good enough to justify subjecting the woman to a section. If the baby should turn out to be Rh-negative, then the section would be unnecessary. In such cases an Rh-positive baby has been exposed to strong antibodies throughout pregnancy, and it is being optimistic to believe that reducing the exposure by three weeks is going to make much difference in the outcome. If one tries to deliver the baby even earlier, then he has two conditions to combat, prematurity and erythroblastosis. It would be a tragedy to lose an Rh-negative baby from prematurity of one's own making.

"When it seems that delivery, say three weeks early, is advisable, labor usually can be instituted by medical induction and rupture of membranes as many of these patients are gravida III or more." The writers have seen nothing to indicate that antibodies are "squeezed out" into the baby as sometimes has been stated in justifying cesarean section over normal delivery.

"It is true, however, that an unsuccessful medical induction may cause more fetal cells to enter the maternal circulation with a resulting increase in antibodies. This may increase the degree of fetal involvement particularly in instances in which the titer has been positive a month or so already."

Treatment of Gonorrhea with Dihydrostreptomycin — JACOBY, ADOLPH, GOLDBERG, WILLIAM, SOBEL, NATHAN AND ROSENTHAL, THEODORE — *American Journal of Syphilis, Gonorrhea and Venereal Diseases*, 34: 185 (March) 1950.

"An investigation to determine the results of treatment obtained with dihydrostreptomycin in patients having gonorrhea is herewith reported.

"In order to simplify the determination of the outcome of treatment, only male patients were included. The ages of these patients ranged from 15 to 40 years with a median of 27.3 years.

"The duration of the infection varied from 1 to 60 days, the majority of patients having had the disease less than 1 week.

"The treatment consisted of a single intramuscular injection of either 0.5 Gm. or

1 Gm. of dihydrostreptomycin. The solution was prepared by adding 1.4 cc. of sterile, distilled water to 1 Gm. of dihydrostreptomycin.

"Eighty-one patients received 0.5 Gm.; 94 patients received 1 Gm. Of those receiving 0.5 Gm., 57 were cured and 3 were considered to be reinfected; i.e., 60 were cured on first treatment. Treatment of 6 failed and 15 patients could not be followed for determination of outcome. Eliminating these 15, 90.9 per cent were cured with a single 0.5 Gm. injection of dihydrostreptomycin.

"The 6 patients whose treatment failed were retreated. Two were cured, 1 by another 0.5 Gm. injection, the other by a 1 Gm. injection. There were 3 failures, 1 on 0.5 Gm. and 2 on 1 Gm. dosages. One patient was lost from observation.

"The 3 whose treatment failed on the second treatment were retreated. One received 0.5 Gm. of dihydrostreptomycin and was cured; 1 was given an injection of penicillin and was cured; and 1 was given 1 Gm. of dihydrostreptomycin and failed to be cured. This last patient was then given an injection of penicillin and was cured.

"Of the 94 patients receiving 1 Gm. of dihydrostreptomycin, 69 were cured and 2 were considered to have a reinfection; i.e., 71 patients were cured by the first treatment. Two failed to be cured and 21 were lost from observation. Eliminating the latter group, 97.3 per cent were cured with a single injection of 1 Gm. of dihydrostreptomycin.

"The 2 patients who failed were retreated. One failed with an additional gram of dihydrostreptomycin and was then given penicillin and was cured; the other was given penicillin and was cured."

"Thirty per cent of patients complained of some pain at the site of injection. Five per cent complained of slight dizziness. One patient who received 1 Gm. complained of syncope and 3 of slight nausea. None of those receiving 0.5 Gm. showed these symptoms. No patient had any febrile reaction or neurologic complication."

The writers' criteria of cure comprised first a disappearance of signs and symptoms; and second, negative urethral and prostatic smears and cultures taken one week after treatment. As a practical measure, they considered all cases with positive findings prior to one week after treatment as failures and those with positive findings after one week of treatment as reinfections.

"The results of this investigation indicate that dihydrostreptomycin is a highly successful therapeutic agent in the treatment of gonorrhea. Although the percentage of cure is slightly greater with 1 Gm. dosage, the statistical variation is not sufficiently significant to favor either dosage."

Oral Penicillin in the Treatment of Gonorrhea — ROBINSON, RAYMOND C. V. — *American Journal of Syphilis, Gonorrhea and Venereal Diseases* 34: 187 (March) 1950.

"In this study, 98 male patients with gonorrheal urethritis were given a single dose of penicillin by mouth in the presence of a physician or a registered nurse. Of this number, only 70 patients were seen subsequent to the treatment day." Results of treatment in these 70 patients are compared to the results obtained with a single intramuscular injection of 75,000 units of procaine penicillin in oil.

"Of 72 patients who were given a single dose of 250,000 units, 55 were seen at least once following treatment. In 11, the discharge persisted. In 44, the discharge disappeared within one to four days. These 44 patients, observed a week after the treatment day, showed no clinical evidence of the disease; and urine cultures at that time were negative in 30 of them."

"Fifteen of 26 patients who were treated with 500,000 units of penicillin orally were observed for a week after taking the drug. Thirteen obtained cures as evidenced by absence of discharge and negative urine cultures.

"In contrast to the above results, 77 of 81 patients treated with a single intramuscular injection of 75,000 units of procaine penicillin in oil were cured."

It was concluded that oral penicillin in a single dose of 250,000 units is not as effective in the treatment of gonorrhea as 75,000 units of procaine penicillin in oil parenterally administered. "In a small series of patients, however, 500,000 units given orally, produced essentially similar results to those following parenteral injection."

Leukopenia of Short Duration as Immediate Reaction in Blood Transfusion Accidents. Second Communication — BUCHER, RUDOLF—*Schweizerische medizinische Wochenschrift*, 80: 349 (April 8) 1950.

The author studied 220 cases in which 300 cc. of blood, preserved according to the Winterthurer method, was transfused within a period of 10 to 20 minutes, partly filtrated and partly without filtration. Blood was taken from the finger of the recipient at intervals of five minutes and a red, white, and differential count was taken. When filtered blood was used the variations of the absolute and relative figures did not exceed the margin of error of the methods of counting. When nonfiltered blood was used approximately one fourth of the recipients showed no appreciable modification of the number of erythrocytes and of the differential count but showed a very definite leukopenia, with a reduction of the number of leukocytes even to one third of the initial value. This leukopenia started partly during the terminal phase of the transfusion itself and partly immediately after termination of the transfusion; it regressed within 30 minutes and after 45 minutes leukopenia was not demonstrable in any case. The lowest leukocyte count was reached on the average, 10 minutes after termination of the transfusion. When blood which had been preserved for only 2 to 3 days was used only 3 out of a total of 100 patients showed a definite leukopenia and in these 3 cases a striking amount of clots was demonstrable in the preserved blood even before transfusion, obviously originating from too slow withdrawal of blood on preparation. These results suggested that the transitory leukopenia was caused by filter residue (coagulated groups of erythrocytes, conglomerations of leukocytes from the leukocytic layer and fibrin clots). The author carried out the following experiments: The filter residues of blood specimens which had been preserved for one week were collected, triturated with sterile saline solution, and suspended in an amount of 0.5 to 2.0 Gm. of wet weight in 20 cc. of saline solution and injected intravenously within one minute. Ten such experiments were made on 5 test individuals. With a dose of 0.5 Gm. of filter residue, 2 individuals showed none or hardly any leukopenia and no change in the red and differential count, while 3 showed a definite though slight leukopenia. With 2 Gm. of residue, all 5 individuals showed a definite and sometimes intense leukopenia; in 1 case the leukocytes diminished from 7,200 to 1,500 within 10 minutes after the injection, without change in the differential count and the red count. In all 8 cases in which leukopenia supervened, it subsided within 30 to 45 minutes, and the author stresses that the duration of the leukopenia was not related to the smaller or larger amount of residue injected. The test individuals who always belonged to the same blood group as the blood residue used, also developed slight oppression and increased respiration immediately after the injection, and later an elevation of temperature.

In another series of 5 experiments the filter residue was lavaged with distilled water until erythrocytes and leukocytes were hemolyzed and no longer demonstrable microscopically; the purified powdered fibrin was dissolved in saline solution in amounts of 2 Gm. and injected in the same manner. The results were the same as with unwashed filter residue. In 5 cross experiments with a suspension of uncoagulated cell detritus taken from the centrifuged water used for lavage in the above experiments and resuspended in saline solution, no influence on the number of leukocytes was observed; however relatively small amounts of sediment were dealt with in these cases. Yet, these experiments indicate that the transitory leukopenia is chiefly caused by the fibrin precipitates of relatively older preserved blood which is richer in clots.

Two transfusion accidents were also studied; in both cases the blood group of the preserved blood (allegedly group A) had not been checked before transfusion because of emergency factors and both recipients had group O; after 50 and 80 cc. respectively alarming immediate reactions occurred. The number of leukocytes fell immediately in 1 case from 8,900 to 3,200, and in the other even from 8,250 to 900, while the red and differential count remained unchanged. Both patients recovered relatively rapidly, and in both the

leukocytes reached the initial values within 40 minutes, and even slightly exceeded it in the second case. Both patients showed hemoglobinuria.

On the basis of these accidents further experiments were carried out on 6 test individuals. Two individuals each of blood groups O, A, and B received 50 cc. of agglutinated citrated heterologous blood agglutinated in vitro with 10 cc. of test serum of the contrary group; that is, those with groups O and B received agglutinated A blood, and those with group A agglutinated B blood; later the same individuals of the A and B groups received 50 cc. of agglutinated citrated blood of their own group, agglutinated in vitro with 10 cc. of test serum of the contrary group. In 9 of the 10 experiments a definite immediate leukopenia supervened, reaching the minimal value within 10 to 15 minutes, with values down to one-half the initial ones in some cases. The initial values were restored within 30 to 45 minutes. Hemoglobinuria was demonstrable in all cases and the red and differential count showed no definite changes. Only in 1 experiment with an individual of group B injected with agglutinated blood of his own group, the leukocytes showed no definite decrease, although a definite leukopenia had occurred in the same case with the blood of the contrary group; hemoglobinuria was demonstrable in this case as well.

Thus not only fibrin clots but also agglutinated erythrocytes produce immediate and transitory leukopenia, and agglutination of erythrocytes undoubtedly occurs intravasationally when wrong blood groups are used in transfusions. The striking immediate reaction is independent of the fact that agglutinated foreign or identical blood is used, indicating that mechanical embolic factors rather than biochemical foreign substances (agglutinins or agglutinable substances) are responsible. These findings undoubtedly had no relations to anaphylaxis, and none of the test individuals showed any other signs of anaphylaxis. No definite change in the differential count and no subsequent hyperleukocytosis was demonstrable. Animal experiments were conducted under the author's direction for determination whether this leukopenia is attributable to the same factors as that discovered by several writers after intravenous injection of glycogen and other substances; these authors were able to prove that the pulmonary capillary circulation, partially blocked by these substances, transitorily retains the leukocytes.

Cause of Death in Meningococcic Infection. Analysis of 300 Fatal Cases — DANIELS, WORTH B. — *American Journal of Medicine*, 8: 468 (April) 1950.

The autopsy protocols and abstracts of the clinical records of 300 patients dying with meningococcic infection in the United States were made available for study. "The cases were analyzed as to cause of death, duration of illness from admission to death and, as far as possible, as to type of treatment used." The three major forms of the infection are meningitis, fulminant meningococcic bacteremia with adrenal hemorrhage and fulminant meningococcic bacteremia without adrenal hemorrhage.

"Analysis of the Deaths from Meningitis.—Of the 144 patients who died from meningitis, only 26 lived 96 hours or longer. The duration of life in this group of 26 patients ranged from 4 to 110 days." In two-thirds a complication caused or contributed to death.

In general, those patients with the more severe meningeal involvements tended to live longer than those with moderate involvement. "It is believed this indicates that since the advent of sulfonamide therapy, death is most commonly due to the effects of bacteremia and resulting 'toxemia' during the early phase of the illness rather than to the meningitis itself.

"Among the 118 patients who died within 96 hours of admission, certain associate lesions were found at autopsy. These were pneumonia in 26, encephalitis in 11, myocarditis in 11, purulent pericarditis in 4, pressure cone in 4, periadrenal hemorrhage in 2, tubular degeneration of the adrenal, meningococcic peritonitis, purulent arthritis, subarachnoid hemorrhage and bleeding peptic ulcer each in 1 of the patients.

"The records of treatment available in the clinical abstracts of the 144 patients from meningitis were not complete so that the total dosage administered is not known. Sulfadiazine was used in 103, sulfathiazole in 13, sulfapyridine in 2, sulfanila-

mide in 4 and antimeningococcic serum alone in 1 of the cases. In 9, there was no record of treatment and in 12 no specific therapy was given. Forty-two patients received other therapy in addition to sulfonamides; namely, antimeningococcic serum 14, meningococcus antitoxin 15 and penicillin 13. In 55 of the 144 cases there were records of the sulfonamide concentration in the blood. The maximal concentrations in these were 52, the average 17 and the minimal 3.5 mg. per 100 cc. of blood. It would appear that at least adequate dosages of sulfonamides had been given to these patients. Six patients were either undiagnosed or diagnosed incorrectly prior to necropsy.

"Analysis of the Deaths from Bacteremia.—More than half of the fatal instances of meningococcic infection resulted from bacteremia. The blood culture was positive for *N. intracellularis* in 94 per cent of the cases in which a blood culture report was available. Hemorrhage into the adrenal was present in 126 and absent in 30 of these deaths from bacteremia.

"Adrenal Hemorrhage Group: In all patients recorded as having hemorrhage into the adrenal gland there was free blood, and no instance of hyperemia is included. . . . Those with minor grades of hemorrhage into the adrenal lived on the average 48 hours after admission to hospital while those with moderate and massive hemorrhage lived an average of 22 and 16 hours, respectively.

"Patients with adrenal hemorrhage survived from a few minutes to 120 hours after admission. Myocarditis was found on microscopic study of the heart in 28 of the patients. It is not surprising, considering the previous rarity of Waterhouse-Friderichsen syndrome, that 14 cases were either incorrectly diagnosed or not diagnosed prior to death."

"In the Waterhouse-Friderichsen syndrome the manifestations of meningitis are usually absent or slight. In almost half of the 126 patients dying with this syndrome there was no meningitis present at necropsy. In an additional 37 per cent meningitis was of mild grade. Less than 15 per cent of the autopsies showed evidence of a moderate or severe grade of meningitis." Table I shows the grade of meningitis, if present, in this grade.

Table I

Severity of Meningitis at Autopsy in 156 Patients with Fulminant Bacteremia

Severity of Meningitis	Bacteremia with Adrenal Hemorrhage	Bacteremia Without Adrenal Hemorrhage
None	61	13
Slight	48	16
Moderate	7	..
Severe	7	..
Unclassified	1	..
No record	2	..
Total	126	30

"Hemorrhage into the adrenal was found at autopsy in 5 patients who during life did not have the usual manifestations of Waterhouse-Friderichsen syndrome. Conversely, among the 30 patients who died from fulminant bacteremia in whom no adrenal hemorrhage was found, 4 patients had shown the classical clinical manifestations of the syndrome. . . . In fulminant meningococcic bacteremia it is difficult if not impossible to be certain on clinical grounds whether or not adrenal hemorrhage has occurred."

Of the 126 patients, 23 received no specific therapy; for 9 there is no record of treatment; for 83, sulfadiazine was used and in 11 others some other sulfonamide was employed. "The average amount of sulfadiazine given on the first day of treatment was 10, the maximal 26 and the minimal 4 Gm. Sulfadiazine blood concentrations were recorded in only 18 patients and ranged from 3.5 to 56 with an average of 16 mg. per 100 cc. of blood. The records of additional forms of therapy are not complete so that the number of patients receiving aqueous adrenal cortical extract, antitoxin, penicillin, plasma, etc., is not known.

"Bacteremia Without Adrenal Hemorrhage: Thirty patients, 10 per cent of all those dying with meningococcic infection, had bacteremia without hemorrhage into the adrenal and with slight or no involvement of the meninges. In 16 there was only slight meningitis at autopsy and in 13 there was no evidence of meningitis. In 1 case, information as to meningeal infection was not available. A diagnosis was not arrived at prior to death in 5 cases. The blood culture had been positive in 75

per cent of the patients on whom reports were available. This group of patients survived for from 2 to 101 hours and died on the average 33 hours after admission. At necropsy diffuse hemorrhages into the serous membranes and hemorrhages into the lungs and other organs not including the adrenals were usual. The treatment in this group was comparable to that given to the group with adrenal hemorrhage. Eighteen of the 30 patients received sulfadiazine. In only 5 patients was there a record of sulfadiazine concentration in the blood. These were 25, 19, 22, 9 and 5 mg. per 100 cc. of blood."

"It would appear from an analysis of these data that when meningococcic infection is treated early with sulfonamides, meningitis is not often the sole cause of death. Those patients with meningitis who died in less than 96 hours probably succumbed to bacteremia and the accompanying 'toxemia' as much as to the meningitis. . . . This again emphasizes the necessity of recognizing that meningococcic meningitis begins as bacteremia. This phase of the disease can be diagnosed by an experienced clinician before the report of a blood culture is available. Treatment in this phase may lower death rates still further."

Some Everyday Problems in Dermatological Practice—UPTON, W. C. T.—*Medical Journal of Australia*, 1: 295 (March 4) 1950.

The writer discusses the treatment of some common skin diseases.

Psoriasis.—One will have no trouble in diagnosing untreated psoriasis, except perhaps in the scalp. "Patients are often referred with seborrhoeic dermatitis which turns out to be psoriasis."

If one finds hard scaly patches in the scalp that do not respond to the usual antiseborrhoeic applications, suspect psoriasis. "Sometimes psoriasis commences in the scalp." The problem now is to know what treatment to use. "There is no certain cure, either internal or external."

The writer's practice is to give patients the following information: (1) The complaint is very common and the majority of patients are greatly helped if they cooperate. "(2) Sometimes the rash disappears for months or years without leaving a mark. (3) As a rule there are no complications, and psoriasis is sometimes called a 'disease of the healthy.' (4) The condition is not infectious."

Psoriasis of the scalp, the writer has found, often clears up more easily than psoriasis on other parts. "Let the application be clean and easy to wash out and not leave any unpleasant odour. A useful prescription is the following: mercuric ammonium chloride and salicylic acid, of each 15 to 20 grains; greaseless base and cold cream, of each equal parts, to 1 ounce. This is rubbed in at night and washed out next day."

"In psoriasis of other areas, always try clean treatment first, so as to avoid staining underclothes, sheets, pillows, etc. The following routine may be tried: (1) the taking of a hot, soapy bath; (2) the rubbing in of the following ointment: Liquor Picis Carbonis, 60 minims; Acidum Salicylicum; 10 grains. Hydrargyrum Ammoniatum, 10 grains; greaseless base to 1 ounce. If this makes no impression, then 'Cignolin' (0.5 per cent) or a substitute should be added.

"The patient should be instructed to report if the treatment causes much irritation, or better still should be inspected at regular intervals. X-ray treatment is clean and usually clears up patches when first used. It does not stop recurrences, and some patients become x-ray addicts.

"If the lesions are very extensive, the patient should be in hospital. In certain cases, particularly in older people, it may be good treatment to leave the complaint alone if the patients are suffering no pronounced physical or cosmetic disability.

"Acne Vulgaris.—One frequently sees a young woman with severe acne on the face causing her great distress on account of her personal appearance. Sometimes she has consulted a practitioner in earlier life who has told her perhaps: 'That is only pimples due to your development, and you will grow out of it.'

"That may be good advice for mild acne, but he should have gone further and added: 'If it gets worse, see me again.' "

In an average case of acne on the face, the writer has used for some years the following procedure: "This procedure is carried out at night. (1) Remove the 'make-up.' (2) Steam the face for five minutes.

(3) Pinch massage for five minutes, avoiding any painful area, especially on the upper lip. (4) Wash the face with hot water and simple soap. (5) Dry the face. (6) Dab on a lotion such as Lotio Sulphurata. (7) Leave off treatment for a few days, especially the lotion, if the face becomes too sore."

For the severe form of acne the writer strongly advises x-ray treatment. It is not a certain cure, but it is the best local treatment. The writer believes in a definite course of treatment within safe limits, and not two or three small doses "just to encourage the patient."

For the average skin in these severe cases the writer has used for years the following factors and technique: 100 kilovolts, no filter, focal skin distance 25.5 cm., half-value layer 1.7 mm. of aluminum, dose 150r; the treatment is applied every two weeks for six treatments.

"When the course has been completed, after-treatment should be carried on, such as avoidance of certain foods, and the procedure as outlined for the treatment of mild acne should be observed."

Certain foods and drugs, such as iodides and bromides, can stimulate the sebaceous glands and should be avoided. Certain glandular products are used, such as stilboestrol, but have been disappointing in the writer's hands.

"Contact Dermatitis.—Contact dermatitis may be divided into two groups for discussion: (1) acute, in which the rash appears with dramatic suddenness; (2) subacute, in which the rash slowly develops.

"Contact dermatitis usually occurs on the exposed parts, as the face, hands and arms. Sometimes it occurs on the covered parts where the skin and clothes become saturated with dusts from chemicals or wood dusts or oils. Idiosyncrasy plays an enormous part.

"The diagnosis of acute contact dermatitis on the face is usually easy because of the presence of redness, oedema, weeping and closure of the eyes.

"Sometimes the cause is not always obvious. A practical point is to ask the patient what he was doing 24 hours before the rash appeared. Was there something new that had been applied to the face or scalp?"

"The treatment in such an acute case is often a problem. Almost anything seems to irritate some patients. . . . Cold compresses usually are the best application in the first place, such as lead and glycerin lotion, boric acid, bicarbonate of soda, normal saline, and a very useful application is equal parts of olive oil and lime water. Burow's solution, 1 part to 20 of water, is sometimes helpful.

"Later, plain oily calamine lotion may be used, or some other bland application such as the following: distilled water 5 parts, Burow's solution 5 parts, anhydrous lanolin 20 parts, zinc paste 30 parts.

"Plantar Warts.—Plantar warts, painful lesions on the soles of the feet, can be difficult to clear up." If one examines a plantar wart one will often find that the deeper surface is more extensive than the outer surface. "This no doubt accounts for recurrences after excision, diathermy and sometimes x-ray treatment.

"For a few well defined warts, x-ray treatment is often successful; but the doses must be adequate, such as 2,000r in divided doses, superficial x-rays being used. If this amount does not effect a cure, the course should not be repeated.

"For multiple warts, especially when the small 'mosaic' type is present, x-ray treatment is out of the question.

"Various chemical methods have been tried." The writer has had a fair amount of success with the following procedure in treating ordinary plantar warts: "(1) Shave the wart and surrounding callus—this is usually painless. (2) Apply a bunion or corn plaster or a piece of ordinary plaster with a hole in it, to the wart, which is thus exposed. (3) Apply the following paste: salicylic acid 360 grains, trichloracetic acid 60 grains, glycerin sufficient only to make a thick paste. (4) Apply a piece of plaster over the area, and leave it on for four days. (5) Repeat the procedure twice—that is, 12 days' application in all. (6) Examine the patient four days after the treatment has been finished. The wart frequently comes away on the plaster, or it may be gently assisted out. If the above described method is not successful, the strength of trichloracetic acid may be increased.

"'Mosaic' warts may be treated by smearing on the paste for a few days and

covering it with plaster. As a rule the paste is well tolerated."

The Problem of Industrial Dermatitis.—"As soon as an employee develops a rash he should be instructed to report to the first-aid department or to a foreman, and should then be referred to the industrial doctor or to his own local medical attendant. If there is a suspicion that the rash is due to occupation, the medical practitioner should take careful notes on the following points: (1) where the rash first began—it may have started on the legs as varicose dermatitis; (2) where the rash is at the time of examination; (3) the nature of the rash; (4) the type of work in which the employee is engaged; (5) whether similar cases occurred with the same type of work; (6) any treatments that had been used.

"Industrial dermatitis usually commences on the exposed parts first—face, hands, wrists and forearms. However, in some cases dermatitis may originate on the covered parts, when the workman's clothes may become saturated with fine dusts, as chemicals, cement, lime, wood dusts or oils. If the medical attendant is not sure of the diagnosis or the cause, he should refer the patient to the certifying surgeon or to a dermatologist for an opinion."

"It must be remembered that frequent mild attacks of dermatitis lower the skin's resistance, and that what may have been easy to cure in the early stages may develop into a real therapeutic problem. In fact, some patients ultimately develop a 'compensation complex,' and cure or a considerable improvement may not occur until the compensation claim has been finally settled."

The writer makes the following further points: (1) If occupational dermatitis is suspected, take the employee off that work at once. "(2) Treat the patient with bland treatment. (3) If the condition has been very mild, or if there is some doubt about an occupational origin, the patient may return to work when he recovers, provided that (*a*) he uses protective creams on the exposed areas and suitable cleansing agents, and (*b*) he reports if a recurrence takes place. In the case of dermatitis of the covered parts, he should have facilities for a hot shower bath and have the baths at lunch and 'knock-off' time. In all dirty jobs hot running water must be provided. If these measures are not successful, then a complete change of job is imperative. (4) Employees with naturally sensitive skins should be regarded as 'risks.' (5) Some employees can be difficult. A few will not avail themselves of the facilities provided. Others feel that a change of job will mean a reduction in wages. Some of this latter group have said . . . . that they would rather continue to work 'at their own risk.' Experience has shown that if this type of workman should become sensitized he has a poor memory, and naturally seeks compensation benefits. These problems must be met with understanding, tact and firmness."

The Problem of Overtreatment.—"The following is a common history: A patient develops a simple rash, and he often rubs in some patent ointment or something recommended by the chemist to 'kill the germ.' Sometimes a patient is referred with the remark: 'I prescribed a little acid salicylic and sulphur in an ointment, this appeared to help at first, but the rash is now getting out of hand.' "

Penicillin cream, Whitfield's ointment, sulphanilamide ointment or powder, or some other chemical has been responsible for changing a simple rash into a long, tedious attack of generalized dermatitis in some cases.

"If the dermatitis is acute, some suggestions about treatment have already been given in the section on contact dermatitis.

"If the dermatitis is not acute, try bland preparations, in the first place, such as zinc paste, zinc cream, or some form of calamine lotion. Should the rash not respond to such simple measures, then it is time to try stronger applications, but not antiseptic ones.

"A practical point and one worth remembering is this: Try the application on a small area first, and extend it only if it suits. Such applications usually contain tar in some form or other."

Superficial x-ray treatment is often of great value, but it should be superficial. "Filtration is not necessary, and the kilovoltage need not exceed 100."

" 'Never use antiseptic treatment on simple dermatitis.' "

Aureomycin in Urinary Tract Infections. Preliminary Clinical Report— RUBIN, SEYMOUR W. AND GOLDSTEIN, ALBERT E. — *Annals of Internal Medicine*, 32: 661 (April) 1950.

"Aureomycin is effective by mouth in genitourinary tract infections. . . . Aureomycin is effective against gram-positive cocci and gram-negative bacilli, especially against *B. coli* and *Aerobacter aerogenes*, the frequent urinary infective organisms."

The writers have used two dosage schedules in their cases and they have varied the duration of dosage considerably since. To their office patients they give 500 mg. oral aureomycin four times a day for the first day (approximately 30 mg. per Kg. average size adult) and 250 mg. four times a day for the next two days (approximately 15 mg. per Kg.).

In the hospitalized patients the writers have given a five day course of therapy beginning with 250 mg. aureomycin every hour for 6 doses, then every two hours for the next 9 doses, then every four hours for 12 doses and finally every six hours for 8 more doses. "This latter schedule represents an initial dose of 3.75 Gm. the first day, 1.5 Gm. the next two days and 1 Gm. on the fourth and fifth days."

"One of the remarkable things about aureomycin is its disinclination to cause any toxicity." Looseness of the stool, however, has been a very frequent finding. "Normal bowel action was again evident after discontinuance of the drug. Next in frequency was the occurrence of nausea, occasionally with vomiting. Only rarely is it necessary to discontinue the use of the drug because of the vomiting; Amphojel helps in these cases. In 1 case of severe nausea and vomiting in a patient with frequent severe migraine headaches, the drug was discontinued for 12 hours and then readministered with return of only mild nausea without vomiting. Dizziness and malaise have also been complained of, as well as dryness of the mouth in 2 cases."

A complication, which has heretofore never been reported, has been observed in a number of the writers' patients— microscopic hematuria with red blood cells in the centrifuged urine, varying from five to loaded red blood cells per high power field. "One case had a frank and rather severe hematuria with the passage of two large clots. . . . . The only positive effect of aureomycin on the kidneys is its mild diuretic action."

The results obtained with the use of aureomycin even in the writers' small series are felt to be noteworthy. This group of 25 patients has only been a "scout" series to determine a dosage schedule, the length of time medication should be persisted in, the type of organisms affected, and the type of urologic disease best controlled by aureomycin.

This has not been an easy series for aureomycin because the writers chose for therapy not recent infections, but the most stubborn cases, infections that have been long standing and which have clinically defied many and varied therapeutic approaches.

"The urologic diseases (of infective nature) treated with aureomycin are varied and include recurrent acute and chronic pyelonephritis, infected hydronephrosis and calculous pyohydronephrosis, urolithiasis, chronic ureteritis and both recurrent acute and chronic cystitis. In addition to some of the obstructive uropathies, many of these patients have had repeated instrumentations, 2 have had recent prostatectomies and 1 a recent ureterolithotomy."

The results were indeed gratifying. "Only 5 cases were outright failures. Of these, 2 were proteus infections and 1 *B. coli*. It has been repeatedly observed that aureomycin is ineffectual against urinary infections due to proteus and pyocyaneus." The writers' cases substantiate this view, although 1 case had a pure culture of pyocyaneus and clinical cure was obtained. "Three patients had satisfactory results but only of a temporary nature. The failure of the case of *B. coli* cystitis to clear might be explained as due to too short a course of aureomycin therapy." The other cases of *B. coli* infections gave satisfactory to excellent results.

"Good results of a permanent nature were obtained in 9 cases and of a temporary nature in 11 more. . . . More cures could have been obtained if the course of aureomycin therapy had been extended over a week or 10 days."

Aureomycin has a bacteriostatic effect rather than a bactericidal effect and in

order for one to accomplish a bactericidal effect, the dosage would have to be increased beyond clinical application. Because of these facts, many good results were of a temporary nature (9 out of 12), with grossly clear urine which became cloudy again after a week or two. "One must therefore be cautious about accepting a cure when the urine becomes clear or microscopically free of pus cells, because frequently a Gram stain of the centrifuged specimen or a culture will reveal the organisms to be still present. Undoubtedly, a longer course of therapy could keep the urine clear and also perhaps permit the natural body forces to overcome the infection and achieve permanent eradication of the infective process.

"Another very important point is brought out in this preliminary short series of cases—the indications for operative urology do not change. Cases of obstructive uropathy demand relief of the obstruction. The presence of foreign substances in the urinary tract demand measures necessary for their removal." None of the cases of urolithiasis derived more than temporary relief and a cure cannot be expected until the calculus is removed, either by operative or nonoperative means. "On the other hand, the utilization of aureomycin in susceptible infective cases favors a better and more permanent result."

One of the "toxic" manifestations which the writers have observed in several of their cases and which has not been reported by others, was the occurrence of hematuria, frank and microscopic. It does not appear that aureomycin is nephrotoxic in any respect; the urine is highly acid, however, during treatment with aureomycin and may remain so for a few days, especially with the higher doses. This acid urine becomes a source of considerable irritation in an enclosed, irritable and inflamed bladder, and it was in the cases of cystitis (in which the acid irritant acted on a sensitive inflamed bladder mucosa) that the writers found hematuria. Similarly, the highly acid urine was the cause of the bladder discomfort in 2 patients. "The discomfort persisted after the discontinuance of the aureomycin. It has been observed that aureomycin is retained in the body and urine longer than other antibiotics."

Amebic Pericarditis. Report of a Case — Carter, Max G. and Korones, Sheldon B. — *New England Journal of Medicine*, 242: 390 (March 16) 1950.

The writers present a case of suppurative pericarditis secondary to rupture of a liver abscess in which the amebic etiology was established after surgical drainage of the pericardial sac.

"Case Report.—A 24 year old Hindu seaman entered the hospital on August 19, 1948, complaining of retroxiphoid and epigastric pain.

"The patient had been well until one month prior to admission, when he noted the onset of moderate anorexia. Two weeks later, he felt a sharp pain in the left shoulder anteriorly, which persisted as an ache, was aggravated on deep inspiration and was not affected by movement of the joint. Twelve days prior to admission chills developed, accompanied by a feeling of feverishness and a dry mouth. One week before admission, a dull, persistent retroxiphoid and epigastric pain appeared and soon spread to the left anterior costal margin and was more severe on deep inspiration. Drenching night sweats and an infrequent dry cough developed during the five days prior to admission. On the day of entry, while walking on the street, he suddenly became weak, collapsed without loss of consciousness and was brought to the hospital.

"The patient stated that he had been born in Portuguese Goa, India, had served in the British Navy for five years during the war, and for the past three years had lived in the United States continuously. He gave no history of diarrhea or other gastrointestinal symptoms occurring at any time during his life. The remainder of the system review was not significant.

"The family history was noncontributory. Two sisters were living and well. The father and mother had died of a fever of unknown type 11 years prior to the patient's illness.

"Physical examination revealed a well developed, poorly nourished man who was acutely and chronically ill and complaining bitterly of pain in the left shoulder anteriorly. The pharyngeal mucosa was slightly reddened. The skin was hot and moist. There was moderate rigidity and

tenderness in the upper abdomen, which was most pronounced in the midepigastrium. Neither the liver nor the spleen could be percussed or palpated below the costal margins. The peristaltic sounds were normal, and there was neither abdominal distention nor costovertebral angle tenderness. The heart and lungs were normal, and the remainder of the physical examination was not significant.

"The temperature was 99.2° F., the pulse 90, and the respirations 20; the blood pressure was 110/70.

"Examination of the blood showed a hemoglobin of 9.0 Gm. per 100 cc. and a hematocrit of 36 per cent. The white cell count was 10,000, with 50 per cent neutrophils, 38 per cent lymphocytes, 4 per cent atypical lymphocytes and 8 per cent monocytes. Urinalyses demonstrated a normal concentration and no sugar or albumin, but occasional white cells and granular casts were present in the centrifuged sediment. The blood Hinton test was negative. The blood nonprotein nitrogen level was 32 mg. per 100 cc. A stool was brown, formed and guaiac negative and contained no ova or parasites. A blood culture taken on admission showed no growth. A lumbar puncture performed on the day following admission revealed a normal cerebrospinal fluid.

"Initial roentgenograms of the left shoulder were interpreted as showing no abnormality. An x-ray film of the chest showed questionable prominence of the left ventricle.

"Chills occurred daily during the first two weeks, and the temperature was irregularly elevated, ranging from 99.0 to 103.0° F. The patient took a soft diet poorly and was given fluids by mouth, barbiturates for sleep and codeine and aspirin to control the persistent pain in the left shoulder and epigastrium. No specific diagnosis was established, but miliary tuberculosis was considered most tenable.

"Further laboratory determinations showed a total white cell count varying from 12,550 to 16,350, and multiple blood smears revealed 61 to 66 per cent neutrophils, 30 to 35 per cent lymphocytes, 2 per cent monocytes and 1 to 6 per cent eosinophils. Examination of the stained blood film demonstrated no malarial parasites. The urine remained normal except for the presence of occasional white blood cells in the sediment. Urine cultures were sterile, as were repeated blood cultures. Agglutination tests of the patient's serum for *Salmonella typhi, S. paratyphi* (B), *S. choleraesuis,* polyvalent dysentery organisms and *Brucella abortus* were all negative. The Weil-Felix reaction was negative. Heterophil antibody agglutination was within normal limits.

"On the fifteenth hospital day, a dull, constant pain occurred in the anterior portion of the right shoulder. This pain was more intense on inspiration, and its character was described by the patient as similar to the persisting pain in the left shoulder. On the following day a harsh pericardial friction rub could be heard over the entire precordium. Intramuscular injection of penicillin was then begun in doses of 50,000 units every three hours.

"A roentgenogram of the chest at this time showed no change from the appearance on admission. An electrocardiogram, recorded on the day after the friction rub appeared, showed only minimal T wave changes. The temperature continued to rise daily to 101° F., and the pulse rate varied from 90 to 110 beats per minute. A roentgenogram of the chest on the twenty-third hospital day showed an extensively enlarged cardiac shadow. An electrocardiogram was consistent with the diagnosis of pericarditis. Distended neck veins, a paradoxical pulse and a diminished pulse pressure were also observed.

"Aspiration of the pericardial sac through a needle inserted in the left costoxiphoid angle yielded 100 cc. of pale orange, purulent fluid, which was creamy in consistence. Examination of the stained sediment from this fluid revealed 150 white blood cells and 50 red blood cells per high power microscopic field. No organisms were found in smears of this pus, stained by both the Gram and Ziehl-Neelsen technics. Bacteriologic cultures of the fluid were sterile.

"Clinical improvement was observed after the pericardial aspiration. This was demonstrated by a fall in temperature, a slower pulse rate and disappearance of the venous distention. Improvement continued for two days, when signs of severe cardiac tamponade returned. Aspiration of the pericardial sac was repeated daily for

the following four days. Fluid similar to that previously withdrawn was obtained in amounts varying from 300 to 450 cc. No organisms were demonstrated by either direct smear or culture of the fluid.

"Penicillin, in a dose of 100,000 units, was instilled in the pericardial sac after each of these aspirations. Parenteral administration of penicillin was increased to 500,000 units every three hours.

"The patient continued to complain of severe epigastric and bilateral shoulder pain, which improved temporarily after each pericardicentesis. He ate poorly, lost weight and looked increasingly ill. On the thirty-first hospital day, eight days after the first aspiration, the pericardial fluid was found to be red-brown and somewhat thicker. Three hundred cubic centimeters of fluid was removed, 60 cc. of air was instilled, and roentgenograms were taken with the patient in various positions to map the pericardium. Pneumopericardiograms demonstrated a thickened pericardium and showed no loculations within the sac.

"Surgical drainage of the pericardium was decided upon because the increasing viscosity of the pericardial fluid prevented adequate relief of the cardiac tamponade by aspiration. Furthermore, a sinus tract developed in the costoxiphoid angle, the site of multiple pericardicenteses. On the thirty-second hospital day, the pericardium was opened by resection of the sternal cartilages of the fourth and fifth ribs on the left side. Local anesthesia was used. The pericardium was marsupialized to the skin of the anterior chest wall. Approximately 1 liter of thick fibrinous creamy material was removed. Both the pericardium and epicardium were thickened, and each was covered by a shaggy, greenish white deposit of fibrin and pus. The blood pressure, which was 80/70 at the beginning of the operation, rose sharply to 120/80 on release of the tamponade. The pathological report of a biopsy of the pericardium taken at operation disclosed 'acute and chronic inflammation in granulation tissue and organizing hemorrhage.'

"The patient improved subjectively after the operation. The improvement in the blood pressure was maintained. However, temperatures varied from 99 to 101° F. by rectum, and the pulse rate remained at approximately 120 per minute. The patient ate poorly. A moderate bilateral pleural effusion, which was greater in the right hemithorax developed, and thoracentesis performed on this side yielded 350 cc. of clear, serous, sterile fluid. The pericardial cavity was irrigated every four hours with half-strength Dakin's solution, and the fibrinous cardiopericardial adhesions were removed digitally once daily. Several blood transfusions were given, and the hematocrit was 42 per cent and the hemoglobin 12 Gm. per 100 cc. one week after the operation.

"On the eight postoperative day, during the digital exploration of the pericardial cavity, a soft area was felt on the floor of the pericardium posteriorly. The examiner's finger fell through this into a large cavity from which welled a considerable quantity of yellow-green, foul-smelling fibrinopurulent material. At that time the diagnosis of liver abscess was established.

"Examination of fresh material from the cavity revealed myriads of organisms identified as *Endamoeba histolytica*. Treatment was then begun with emetine hydrochloride in a daily intramuscular dose of 0.06 Gm. (1 grain). The need for adequate dependent drainage of the liver abscess was realized as the patient's condition grew worse. Therefore, on the tenth postoperative day, the liver abscess was drained through a left subcostal approach, local infiltration anesthesia being used.

"On the following morning (the forty-fifth hospital day), the patient's condition appeared unchanged. However, just before his wound was dressed, he suddenly died. No immediate cause of death was apparent.

"Permission for autopsy was obtained with difficulty. It was learned that the patient had deserted a cargo ship and, contrary to his assertion, had been living in the United States only six weeks prior to admission to the hospital.

"Postmortem examination, performed six weeks after death, revealed two small liver abscesses. One, measuring 5 cm. in diameter, was situated in the left lobe of the liver directly beneath and communicating with the pericardial sac through an aperture approximately 1.5 cm. in diameter. A second abscess, measuring 4 cm. in diameter, was situated in the lower portion of the right liver lobe near the anterior sur-

face. The opened pericardium was thickened, shaggy and adherent to the anterior chest wall. The pericardial sac contained about 20 cc. of thick, gray fluid. There were no adhesions to the heart. The epicardium was thickened and fibrotic, but the heart was otherwise normal. Approximately 300 cc. of serous fluid was present in each pleural cavity. Both lungs were fixed to the mediastinum and to the surface of the diaphragm by dense fibrous adhesions. Neither the lungs nor the mediastinum was otherwise remarkable. Examination of the entire gastrointestinal tract revealed no evidence of disease.

"Extreme postmortem degeneration was evident in all the tissues on microscopic examination. The pericardium was thickened, edematous and infiltrated with mononuclear cells and numerous degenerated trophozoites of *E. histolytica*. The epicardium was thickened by a superficial fibrin layer, which contained degenerated trophozoites and by a subjacent organized layer infiltrated with mononuclear cells. A slight increase of loose connective tissue and a scattered infiltration with lymphocytes were present in the myocardium. The pleura was slightly edematous and fibrotic. The alveolar spaces contained pigment-bearing macrophages, a few red blood cells and round cells. No trophozoites were found in either the lungs or the pleura. The walls of the liver abscesses were necrotic and contained a few inflammatory cells and many degenerated trophozoites. No significant pathological changes were evident in the microscopic sections of the remaining organs."

"The primary complaints of epigastric, infracostal and left shoulder pain form some substantial basis for a possible diagnosis of liver abscess. The persistent evidence of infection, the pain from diaphragmatic irritation, the absence of pulmonary findings and the negative bacteriologic studies suggest liver involvement. Because of the patient's race and foreign origin, enteric pathogens were sought, and he was carefully questioned about antecedent dysentery. However, a negative history is not always significant since half to two thirds of all patients with hepatic amebiasis give no history of antecedent diarrhea. Furthermore, liver involvement has occurred as late as 20 to 43 years after the primary symptoms of diarrhea due to amebas. It has been shown that only 11 to 36 per cent of patients with amebic hepatic abscesses pass amebas in their stools. Even a series of negative stool examinations does not exclude the diagnosis of hepatic amebiasis. Failure to find amebas in aspirated fluids does not exclude the diagnosis either, since the organisms are present in the fluids of only 16 per cent of liver abscesses caused by *E. histolytica*.

"The complement fixation test is valuable, and should have been performed in the case reported above. This test may be negative in the carrier or asymptomatic patient, but it is positive in 90 per cent of patients with hepatic or pulmonary amebiasis.

"In 5,000 cases of amebic liver abscesses collected from the literature, treatment by aspiration resulted in a mortality of 5.6 per cent, whereas treatment by open drainage resulted in a mortality of 43.1 per cent. Open drainage is recommended only for advanced liver abscesses that are secondarily infected at the time of diagnosis. The importance of early diagnosis is apparent. Adequate treatment should result in cure of most of these patients before perforation of the liver abscess occurs."

Diffuse Chronic Glomerulonephritis with Predominance of the Nephrotic Type (Intracapillary Form) — ZOLLINGER, HANS U. — *Schweizerische medizinische Wochenschrift*, 80: 300 (March 25) 1950.

The delimitation of nephritis and nephrosis has been reexamined recently and some authors went as far as to interpret nephrosis as a special type or phase of diffuse glomerulonephritis and to deny the distinction between the two affections; the author has encountered cases in which the distinction between nephrosis and nephritis was difficult clinically and even anatomically, yet he came to the conclusion that there exists a basic difference between the two prototypes of diffuse glomerulonephritis and genuine lipoid nephrosis. The existence of borderline and transitional forms should not lead to abandonment of a fundamentally correct principle of distinction between two affections.

The author reports an illustrative case of a man aged 18, who had suffered for

three years from the typical signs of nephrosis with edema and albuminuria; the syndrome had started insidiously. Three weeks before death uremia with hypertension supervened. The histologic renal findings were peculiar. The surface was slightly undulating, and the capsule was not thickened. The glomeruli showed abnormally gross lobulation, caused by fusion of loops. The latter showed a thickened basal membrane with frank fragmentation. The endothelium but not the mesothelium was proliferated. The lumen of the loops was partly still patent in most cases and contained rather numerous erythrocytes. The mesoangium was widened and rich in nuclei, and contained rather numerous collagenic fibers and abundant argyrophilic fibrillae. Plasma cells and lymphocytes were encountered only in small numbers. Numerous glomeruli showed hyaline transformation. There was a peculiar almost complete absence of proliferation of the capsular epithelium (half-moons) which are the most typical sign of subacute and chronic glomerulonephritis. There were only few synechias between loops and capsule. The tubules showed the typical picture found in genuine lipoid nephrosis, usually with dilatation but occasionally with atrophy; their epithelium showed marked hyaline and drop-shaped alterations and was loaded with neutral fat and double-breaking lipoids. A moderate number of casts was encountered. The interstitial tissue showed rare small lymphocytic infiltrations at the borderline between medulla and cortex and otherwise slight diffuse connective tissue widening, here and there with small nests of lipoid-containing cells. The arteries and arterioles were completely free of inflammatory or fibrinoid lesions but showed moderately intense elastosis; the intima showed no connective tissue widening.

The author interpreted this case as diffuse, chronic, purely intracapillary glomerulonephritis; the question then arises whether in all, or at least a great number of cases, a chronic-nephrotic course without or only with terminal signs of hypertension and excretory impairment corresponds to this morphologic type. Therefore, the author collected and compared his material of intracapillary glomerulonephritis and of cases with a nephrotic course, a total of 12 cases; there were 9 males and no predominance of young individuals could be determined. The history showed a preceding acute glomerulonephritis in only 3 cases; 1 patient had been hospitalized for cystopyelonephritis 17 years before death, but there was no reason to suspect that a glomerulonephritis had been overlooked at that time. Two patients had experienced tonsillitis. In 1 case the nephrotic syndrome developed after an enteritis. In the remaining 5 cases no history of infection or kidney disease was suggested. Albuminuria seemed the earliest and most constant clinical sign and was intense. Edema was the reason for medical consultation in all but 1 of the cases. With 1 exception hypertension did not appear until the last months or even weeks of life. Cardiac hypertrophy was found in 7 out of 10 autopsied cases; in 2 cases only histologic material was available for examination. An insidious course generally predominated until the terminal phase. Two patients showed definite clinical recurrences of glomerulonephritis; in 1 of them a slightly increased strain on the kidneys due to an intestinal infection with jaundice made the latent renal insufficiency manifest. In concordance with the clinical syndrome the cause of death was severe uremia in 11 cases while 1 patient succumbed to a hemorrhage from an aneurysm of the right middle cerebral artery. Four of the autopsied cases showed definite contracted kidneys, 2 showed slight reduction of the parenchyma, in 3 cases the weight of the kidneys was normal, and in 1 case the kidneys were enlarged, macroscopically suggesting nephrosis. In all but the last case the surface was nodular, with pale yellow nodules and dark red depressions. On section the cortex was usually narrowed and the delimitation from the medulla was always blurred. Thus the aspect did not differ from the picture of the so-called secondary contracted kidneys of chronic glomerulonephritis. Histologically, all cases corresponded to the 1 described above, and marked, old proliferation of the capsular epithelium corresponding to the age of the lesions of the loops was not demonstrable in any case. Marked hypertonic vascular damage as otherwise frequent in chronic glomerulonephritis in the form of arteriosclerosis or arteriolosclerosis was lacking,

and there were no signs of genuine chronic interstitial nephritis.

A glomerulonephritis was definitely dealt with anatomically and as almost all glomeruli were involved the affection must be classified as diffuse chronic glomerulonephritis. The otherwise characteristic proliferation of the capsular epithelium was pushed into the background and the term of an intracapillary form of glomerulonephritis seems applicable. In 1 of the author's cases the inflammatory alterations of the intracapillary glomerulonephritis had subsided almost completely and the loops were extensively hyalinized; an extracapillary attack resulted in death. According to the histologic findings the first intracapillary attack must have dated back much farther than suggested by the history of one year's duration, and probably a second attack had occurred at that time; the extracapillary lesions, on the other hand, could not have dated back a whole year. A total of 5 cases showed such extracapillary attacks introducing and probably causing the terminal stage, and thus only 3 of the 12 cases showed neither severe contraction of the kidneys nor acute extracapillary attacks as cause of the terminal uremia.

In acute glomerulonephritis the inflammatory process is limited to the walls of the loops and the capsular epithelium starts only secondarily to proliferate in the subacute and chronic forms; this secondary reaction seems to have been lacking in the cases under consideration; prolonged patency of the capillary lumen constitutes another peculiarity of intracapillary glomerulonephritis, and only the excretory impairment of the terminal phase seems to be attributable to impairment of the glomerular blood supply; the same applies to the hypertension which must be attributed to renal anemia. In the absence of appreciable narrowing of arteries and arterioles the cause of the renal ischemia must be looked for in the glomeruli. The nephrotic course over a period of years must be explained on the basis of the deviating glomerular findings, and renal ischemia from closure of loops must have appeared only late in the course of the affection. The patency of the capillaries is attributable partly to the unusually slight endothelial proliferation and partly to the lack of compression of the loops by the half-moons.

The causes for the appearance of the nephrotic syndrome in renal affections have not been fully elucidated. In pure lipoid nephrosis the author maintains the conception of a primary extrarenal metabolic disturbance; the renal lesion would be the result rather than the cause of the metabolic disturbance. Primary metabolic disturbances of various types have been shown to lead to glomerulonephrosis, and according to recent experimental work the tubular lesions are the result of increased glomerular permeability (glomerulonephrosis) as proteins which have passed into the glomerular filtrate are partially reabsorbed in the tubules. Disturbances of the glomerular permeability will be mirrored in the tubular absorption. This is actually the case in intracapillary glomerulonephritis, and the proteinuria is the central fact in this process. Various geneses have to be considered. Due to a primary metabolic disturbance pathologic proteins may circulate in the blood and may be excreted because of their small molecular weight (the limiting value is 68,000); this genesis is exemplified by febrile albuminuria, the initial stage of lipoid nephrosis, and experimental chicken protein nephrosis. The glomeruli may be damaged by infiltration with proteins to such an extent that they let normal plasma proteins pass (glomerulonephrosis), this genesis is exemplified by amyloid nephrosis, and the chronic stage of lipoid nephrosis. Finally in chronic capillarity of the loops the glomerular filter is also damaged and plasma proteins will pass into the filtrate.

In the cases under consideration the chronic capillarity of the loops explains the albuminuria satisfactorily, but the causes of hypercholesterolemia, hypoproteinemia and edema will still have to be elucidated. These cases indicate that the old therory of chronic urinary loss of protein as cause of a metabolic disturbance and thereby of the edema cannot be rejected as completely as generally done at present, and there are definite analogies to nutritional hypoproteinemia in hunger edema.

The question has to be raised why halfmoon formation was virtually absent in the cases under consideration. It is gen-

erally assumed at present that diffuse glomerulonephritis develops on the basis of an antigen-antibody reaction, and possibly the renal parenchyma and particularly the glomerular tissue represents the antigen. It may and should be admitted that this reaction may be dampened under certain conditions, and the inflammatory glomerular reaction to such an attenuated reaction must be expected to be correspondingly slight, accounting for lack of a capsular reaction and for an abnormally slight endothelial proliferation with lesser narrowing of the capillary lumens. This seems to the author the only acceptable hypothesis as the 5 cases with recent extracapillary attacks and definite half-moon formation demonstrate clearly that there is no fundamental difference between the intracapillary and the ordinary extracapillary diffuse glomerulonephritis.

A protracted course of intracapillary glomerulonephritis is definitely established. According to statistics on 120 cases of chronic glomerulonephritis 54 per cent of the patients showed a typical nephrotic stage, and only 26 per cent none at all. The author's 12 cases represent a selection from about 130 cases of diffuse glomerulonephritis; the appearance of a nephrotic stage in diffuse glomerulonephritis must not under any circumstances be considered as sign of the purely intracapillary form as the latter is much rarer, and the nephrotic stage must simply be considered as expression of a severe lesion of the loops with still preserved permeability. There is no basic difference between intracapillary and extracapillary glomerulonephritis either genetically or functionally, and the intracapillary type is merely a variety of the common type of glomerulonephritis.

Some authors go as far as to consider lipoid nephrosis as subthreshold variety of chronic glomerulonephritis; every case of lipoid nephrosis would then terminate in diffuse glomerulonephritis with hypertension provided the patient lives long enough. The author opposes this conception decidedly; none of his patients with either intracapillary glomerulonephritis or with extracapillary glomerulonephritis with a nephrotic syndrome succumbed to an infection, as is almost the rule in patients with lipoid nephrosis (pneumococcic peritonitis). Among 16 cases of pure lipoid nephrosis the author saw a negligible rise of blood pressure in only 1, and terminal uremia is extremely rare. The histologic picture also differs fundamentally; chronic glomerulonephritis, whether the extracapillary or the intracapillary form, constantly shows a definite fragmentation of the basal membrane while true lipoid nephrosis does not show this fragmentation but rather homogeneous thickening as also observed in other glomerulonephroses. However special membrane stains on thin paraffin sections are required for this differentiation. Although genuine lipoid nephrosis is rare and although it may be impossible to distinguish it clinically from chronic intracapillary glomerulonephritis its existence should not be doubted; such doubt would paralyze further work on its cause which should be looked for in disturbances in the protein metabolism.

The Value of Miniature Radiography in the Detection of Heart Disease — MATHISEN, ARNE K., MORRIS, WILLIAM AND WILSON, G. B. — *American Heart Journal*, 39: 505 (April) 1950.

A short preliminary survey was attempted to demonstrate the value of the miniature film in the detection of heart disease. "During the months of December, 1948 and July, 1949 all 4-by 5-inch films taken at the Vancouver Unit of the Division of Tuberculosis Control of British Columbia were examined for abnormal cardiovascular shadows. Patients whose films were suspicious were asked to return for further study. Every person who was recalled was given a clinical examination, and a 14-by 17-inch film was taken. Fluoroscopy and electrocardiograms were done when indicated."

"From a total of 7,093 films, 158 were selected as showing abnormal cardiovascular patterns. Ninety of these were found to have definite heart disease. The types of heart disease were hypertensive cardiovascular disease (42), arteriosclerotic (15), rheumatic heart disease (26), congenital heart disease (6), and thyrotoxic heart disease (1). Thirty-three patients were unaware of existing heart disease and a number of others who knew of their lesion did not attribute their present symptoms to it. In the same period only 22 cases of tu-

berculosis were discovered; 13 active and 9 apparently arrested.

"Sixty-eight of those recalled had no evidence of heart disease. Several causes were responsible for this high percentage of error. Allowance must be made for the greater distortion at the distance of 48 inches from the x-ray tube focus as against 60 inches. Pregnancy and sthenic build with a high diaphragm made the heart appear enlarged in the miniature films. Scoliosis and a depressed sternum caused a deceptive appearance of enlargement. With increasing experience and more careful study of the films, a much greater accuracy is possible."

"These findings indicate that the mass chest x-ray survey is an excellent method of case finding in heart disease as well as in tuberculosis. It is important that all available clinical information which can be obtained from the miniature film be utilized and that the patient be referred for proper treatment for any abnormality which may be discovered."

Vitamin B_{12} in Idiopathic Steatorrhoea — TUCK, I. M. AND WHITTAKER, NORMAN — *Lancet*, 1: 757 (April 22) 1950.

"The following cases of idiopathic steatorrhoea are reported because they did not respond to adequate dosage of a preparation of vitamin B_{12} known to be active in cases of Addison's anaemia but they recovered promptly with ordinary doses of folic acid. It is of interest that the commercial preparations of vitamin B_{12} are advertised as effective in the anaemia of the related condition, sprue."

Case 1.—A housewife aged 25, in her third pregnancy, was admitted to the hospital eight days before the expected date of delivery because albumin was found in her urine. "The first pregnancy had produced a living child at 40 weeks, but her second baby had died two months after delivery at 36 weeks. The mother's blood was group A, rhesus-positive. She said she had always been anaemic and had taken 'Fersolate' tablets as a routine in all three pregnancies, though apparently laboratory tests of her blood were not done during the pregnancies or at other times. She had never noticed any diarrhoea.

"Labour was induced, on the day after admission, by artificial rupture of the membranes, and the placenta was expressed from the cervix under thiopentone anaesthesia. Labour lasted three and a half hours, and 48 ounces of blood was estimated to have been lost. The first blood count, two days after delivery, showed 1,560,000 red cells per c.mm., Hb 34 per cent, colour index (C.I.) 1.1, mean cell diameter (M.C.D.) 7.8 μ, mean cell volume (M.C.V.) 92 c.μ, and mean corpuscular haemoglobin concentration (M.C.H.C.) 25 per cent; 6,300 white cells per c. mm. (polymorphs 84 per cent, lymphocytes 16 per cent). A transfusion of the packed cells from 880 ml. of compatible blood of group A was given, but three days later the Hb was only 40 per cent. Ten days later it was 38 per cent, though the patient had been receiving 135 grains of iron and ammonium citrate daily by mouth. Her temperature was 102.4° F. seven hours after transfusion, and this was thought to be a transfusion reaction, but neither jaundice nor haemoglobinuria was found. The sternal marrow was megaloblastic, and free hydrochloric acid was found in the gastric juice without histamine stimulation. At this stage no physical signs were present except a sore and smooth tongue."

"The patient was given vitamin B_{12} 20 μg. intramuscularly, but at the end of 13 days there was no reticulocytosis and no rise in the cell count or Hb and the bone marrow was still megaloblastic. The patient remarked that her tongue was no longer sore. At this stage a blood count showed 1,310,000 red cells per c. mm. and Hb 31 per cent. The reticulocytes had been counted daily and were never more than 1 per cent. The patient was then given folic acid 30 mg. daily by mouth. On the fifth day she had a peak reticulocytosis of 18.8 per cent, and after 24 days of this treatment a blood count showed 3,240,000 red cells per c. mm. and Hb 64 per cent. The bone marrow was normoblastic 14 days after the start of the folic acid. On the twenty-fourth day the dose of folic acid was reduced to 10 mg. daily by mouth, and the patient was discharged 13 days later with Hb 70 per cent and 3,690,000 red cells per c. mm. A four day fat absorption test showed only 88.2 per cent absorption. The blood sugar curve was low and flat."

Case 2.—A married woman aged 30, was first seen in the outpatient department of the hospital in August, 1948, when she was complaining of five or six months' pallor and two weeks' soreness of the tongue. "She also had dyspepsia, which began soon after meals, and she had lost weight. Her bowels were regular, and there was no diarrhoea. Her menstrual periods were also regular, lasting 4 to 5 days every 28 days. She had had one child six years previously and no miscarriages. She said she had always been anaemic since adolescence. A blood count showed 3,780,000 red cells per c. mm., Hb 64 per cent, and C.I. 0.85. Of three stools examined for occult blood the first gave a weak positive and the others were negative. She was given fersolate 6 grains t.d.s. and one 'Multivite' tablet t.d.s. and asked to return, but she did not keep the appointment. She attended her private doctor and was given several short courses of iron tablets, but this treatment had been discontinued for about six months before she again came to hospital in October, 1949, 14 months after the first attendance. She now complained of two months' increasing shortness of breath with tiredness and weakness of the legs.

"A blood count (October 10) now showed 1,080,000 red cells per c. mm., Hb 34 per cent, C.I. 1.5, P.C.V. 17 per cent, M.C.D. 8.4 μ, M.C.V. 140 c.μ, and M.C.H.C. 28 per cent. The patient was pale, with a yellowish tinge of the skin and sclerotics and pallor of the mucosae. Her nails were brittle but not spoon-shaped, and her tongue was pale and smooth. There was no oedema, and the liver and spleen were not enlarged. The central nervous system showed no abnormality beyond sluggish knee jerks. The sternal marrow was megaloblastic, with the granulocyte series showing the changes associated with pernicious anaemia. A fractional test meal gave a normal free acid curve, and histamine provoked a well marked response."

"On October 19 a blood count showed 930,000 red cells per c. mm., Hb 29 per cent, and reticulocytes less than 1 per cent. The patient was given 20 μg. of vitamin B_{12} intramuscularly, and though there was a slight reticulocyte rise on the fourth day (3.5 per cent) there was no appreciable change in the haemoglobin or red cells. On the seventh day she was given a further 20 μg. of vitamin B_{12} of proved potency, but no response was obtained, and since on the thirteenth day a blood count showed only 730,000 red cells per c. mm., Hb 22 per cent, and less than 1 per cent reticulocytes it was concluded that none could be expected.

"At this time there was some filling of the neck veins, and transfusion was thought necessary. Packed cells from 2 pints of blood were given slowly over eight hours, and next day the red cell count was 2,100,000 per c. mm. and Hb 40 per cent. A course of folic acid 20 mg. daily by mouth was started, and the reticulocytes reached a peak of 12.5 per cent on the fifth day. This dose was maintained for 25 days, by which time the red cell count had risen to 3,320,000 per c.mm. and Hb to 66 per cent. The patient was discharged six days later on a maintenance dose of 10 mg. of folic acid daily and with a normoblastic marrow.

"In view of the findings in case 1, a four day fat absorption test was done, which showed only 80 per cent absorption. The blood sugar curve was flat. The blood calcium was 9.2 mg. per 100 ml."

The Granny Racket — OGILVIE, HENEAGE — *British Medical Journal*, 1: 683 (March 25) 1950.

"Science is no longer the concern of scientists alone; for the welfare, even the survival, of any State depends upon the proper use of scientific research." Thousands of workers are needed to get details settled and millions of money to provide the apparatus for mass research, and only very wealthy bodies can provide that help. "The really vital question is not whether the State takes part in the future development of a medical service, but, if and when it does so, what part it will take."

"This question confronts the American medical profession today. The more courageous among them realize that now, while the sun of prosperity still shines, they have a unique opportunity to plan a health service along lines of their own choosing, to work with their Government as partners rather than as servants, to extend their research on national lines to unimagined goals. Others . . . . care for none of these

things, but shut their eyes to the facts around them. Such men find Harold Stassen's articles in the Reader's Digest, which many . . . . have read with amusement, meat and drink. 'Never, Never, Never,' in January is a study of the British Health Service based on interviews with discontented doctors and a few slightly inaccurate figures. 'Granny is Gone,' in the February number, tells the story of the old lady who died of pneumonia because she could not be found a bed under the National Health Service. Both articles pay little more than lip service to veracity, but they encourage the American reader to thank God he is not as other men are, and to turn over again and go to sleep.

"The facts are these: The large American hospitals which are not State owned or limited to paying patients are 'in the red.' They are facing a loss that increases every year, and they are increasingly worried over it. The poor American is worse off than Granny, for he gets very little unless he pays for it. He cannot get a nurse to look after him at home, as Granny could have done at the Government's expense. He has never had those necessities that have always been available to the poorest in Britain, even before 1948—unlimited blood transfusion and unlimited chemotherapy.

"It is claimed that 50 per cent of Americans are covered against the cost of sickness by insurance. . . . A fit man can insure against the cost of his first illness or his first operation for a reasonable sum. Once he has been in hospital he can reinsure only at a considerably enhanced premium, or with the more probable risks excluded. When he is really ill he is uninsurable. It is claimed also that those who are so insured can get the best that American medicine has to offer; unfortunately, they may easily get the worst."

"Of all branches of science, medicine concerns the State most closely, for it affects the health, happiness, and working efficiency of every one of the human units that make the State. It is to the State's own interest to see that every man who has some idea or method that promises to advance medicine is given every facility to develop his invention and to apply it for the good of his fellows. It is equally to the advantage of the State to ensure that every citizen, however poor, shall find available to him the best treatment that modern medicine can offer. All men would agree on the truth of these two propositions; it is in the application of them that disagreement is not merely possible but inevitable. Nowhere is help more needed than in medicine; nowhere is control more disastrous."

"The high standards demanded by modern medicine and surgery can be reached only in a hospital, and, as more diseases become amenable to treatment and more people come to know what medicine can offer, the number of hospital beds needed for any unit of population increases. Hospitals are growing in numbers, in size, and still more in the complexity of the departments grouped within them and in the cost of their construction and maintenance. . . . The support of hospitals and the maintenance of research must in future fall upon the largest kind of corporate body, either professional or State."

"The matter of State aid concerns every kind of problem, and its dangers are apparent even to those who insist most strongly on its necessity. It is very much to the fore in Britain, where the State owns every kind of communication, including the postal telegraph and broadcasting systems, every kind of transport, the mines, and many of the major industries." In each case, one is facing the great difficulty of combining State help with efficient management and progressive policy, of seeing that control shall not on the one hand be at the mercy of the changing politics of the moment, and on the other fall into the hands of a permanent bureaucratic clique. Many methods of organization are under trial, and they are all undergoing modification, and, the writer hopes, improvement. "The American medical profession has the unique advantage of being able to study these human experiments in progress, if they will study them, without suffering the pangs of the laboratory animal, of being able to learn what is good and what should be avoided."

What is good in this system is apparent —that the expense of medical care, education, and research will in the future be provided from public funds. "What is unsatisfactory is equally apparent—the waste of money on unnecessary transport, on ex-

pensive apparatus that is not wanted and not cared for, on the administrative hordes that have settled on the body of British medicine and are costing more than the care of the sick. What is bad is as yet feared rather than apparent, and, given wisdom and a willingness to amend abuses as they appear on the part of successive Ministers, it may never happen. The disaster that is greatly to be feared in any State medical service is the loss of freedom —freedom for the doctor to follow truth where it leads him, freedom for the patient to seek help where he has confidence. For the preservation of this freedom two things are essential: first, that all purely professional matters concerning medical education, the staffing of hospitals, and methods of treatment shall be decided on the advice of professional bodies chosen not by the Ministry but by the profession themselves; and, secondly, that private practice must continue."

"One of the most unfortunate things about the inception of a medical service is that it imposes a rigid and artificial system of grading. Grading is inevitable in medicine, but just as in boxing or lawn tennis a man's grading is that which he makes for himself, so in medicine a doctor's grading is the position he attains in the eyes of his fellows and his patients. Academic training, degrees, honours, appointments, publications, all these things count, but they count little beside that indefinable quality a man's real worth."

It is important that the relation of confidence between the doctor and his patient should not be disturbed. "The patient should look on his doctor as an individual whom he has chosen to help his own individual needs, as a man of power who can invoke State assistance and command State resources, never as an official at the end of an office string. For this relationship to be maintained it is essential that private practice should be encouraged rather than driven into the hands of the small group of charlatans who would still exist to prey on the stragglers of a society in which all reputable doctors were perforce full time employees of the State. In matters of decisive concern to the individual—his health, his house, his legal affairs, his money—it is essential that each man should be free, if he so desires, to seek advice from an expert of acknowledged position and integrity, chosen by himself. Only when such a body of experts is available, as a standard for comparison and as a Court of Appeal in doubt or difficulty, can a Government service be wholly efficient or command complete confidence. It is clearly in the interests of a State medical service that the men who work within it, and the men whose wisdom or whose contributions to science have earned them a position in which they are sought as second opinions, should be the same."

"American medicine is at the crossroads, and American doctors would be wise to face that fact. They can see, if they will look, other nations proceeding along, or being dragged along, some of the many paths that lead from the crossing. They are still free to choose their own. They can pick the good and reject the bad from other systems if they will study them, and from these pickings they have today an unparalleled opportunity, one that will never come again, to produce their own system and make it work. They can then go to their Government and say, 'Here is a plan that we, the doctors of America, have devised and tested. We claim that it will keep our scientific research in the forefront of world progress, that it will allow every man who enters medicine to find that work to which he is most suited by inclination and ability, and that it will enable every citizen of our great country to get the treatment that his disability demands. We can prove that the cost of this system to the country is less than that of the National Health Service in Great Britain, that the benefits it confers are greater, and that it is more readily adaptable to changing needs. We ask you to take it over as a going concern. We will run it for you.'

"The organization of medical services must come, all over the world, and the best people to initiate and develop such a public service are the doctors themselves. They alone have a clear and consistent grasp of the true relation of those services to the people, which is essentially that of servant and master—meaning that the true centre of interest and action is not in the authority but in the patient. And that patient is not a number in an office, but a unique person, a living soul." It is be-

cause doctors, and especially that most responsible of doctors the general practitioner, can never forget that all-important fact, so easily mislaid in offices and ignored by Governments, that the writer hopes the American profession itself will take the first steps in its own development on a modern nationwide scale. "Will it do this? Not if it goes on worrying over Granny."

Trihexyphenidyl in the Treatment of Parkinsonism. First Results. Preliminary Note — BARDECI, CARLOS A. — *La prensa médica argentina*, 37: 607 (March 24) 1950.

The new synthetic antispasmodic drug trihexyphenidyl or 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride is also known under the commercial name of artane, produced by Lederle. The author had only a small amount of the drug at his disposal and could study it only on 4 cases but his results amply confirm those obtained in the United States. The first difficulty is encountered with respect to an objective evaluation of the drug effect in parkinsonism. Careful observation of such patients shows that various factors influence the condition, including general health, climate, environment and effective conditions. The conclusion has been drawn that objective evaluation at one given moment has little value and that the sum of daily observations by the patient himself and by his surroundings is a better index of efficacy of treatment than objective tests. On this basis, the author agrees with another writer, who affirmed that patients who have tried many drugs obtain equal or better results with the new drug, without the disagreeable side effects of other drugs. Trihexyphenidyl has been shown to have a certain mydriatic and antisialorrheic effect, and its antispastic effect is manifest on isolated intestinal loops. Clinical and experimental findings demonstrate its rapid elimination and harmlessness. The manner and site of action are unknown.

The author's material included 3 men and 1 woman. One patient had encephalitic parkinsonism of seven years' standing, 2 had idiopathic parkinsonism and 1 had arteriosclerotic parkinsonism with serious arterial hypertension. In the latter cases the affection was of one and a half to six years' standing. At first, a dose of 1 mg. was given four times daily before meals, and after careful observation for toxic effects the dose was increased by 1 mg. at a time, up to a maximum of 9 to 10 mg. The tolerance was good in all cases; the following disturbances have been reported as common: dryness of the mouth; nausea of short duration shortly after ingestion of the drug; a sensation of cephalic emptiness during the period of absorption; occasional nervous conditions. The results were striking in the 3 cases of cryptogenetic-arteriosclerotic parkinsonism while the result in the case of encephalitic parkinsonism was less satisfactory, only some reduction of the muscular hypertonia having been obtained. The intense tremor of the upper limbs in the encephalitic parkinsonism was not influenced by the treatment. The most noticeable effect of the drug in the other cases was relaxation of the hypertonic muscles, and a definite increase of the motor initiative of the patients, either as direct consequence of the relaxation or due to a stimulating effect of the drug; movements became easier, and every day acts such as eating, dressing and turning the pages of a magazine were facilitated. One patient was able to walk steps unaided after a few days of treatment while he had been unable to do so before; it had required 12 seconds for him to do 10 flexions and extensions of the elbow before treatment while he could do them in 5 seconds with a dosage of 6 mg. of trihexyphenidyl. Another patient had a tendency to fall backwards and lost this tendency with a dosage of 8 mg.; when treatment was discontinued for several days he was unable to walk, in spite of administration of tolserol, atropine-scopolamine and daily injections of sulfanesia. The patient with arteriosclerotic parkinsonism experienced marked improvement with a dosage of 4 mg.; he was able to eat by himself which he had been unable to do for a year and developed euphoria. The stimulating effect may reach the stage of nervousness and restlessness as observed in 1 patient with a dose of 10 mg.

On the basis of this limited experience trihexyphenidyl seems to be the optimal treatment of parkinsonism to date, particularly of the idiopathic and arteriosclerotic types.

Pediatrics

The Diagnosis and Treatment of Tuberculous Meningitis in Children — LINCOLN, EDITH M. AND KIRMSE, THOMAS W. — *American Journal of the Medical Sciences*, 219: 382 (April) 1950.

The character and duration of the prodromal symptoms of tuberculous meningitis were studied in a group of 167 unselected cases. "It was found that the early symptoms of tuberculous meningitis are those often seen in children with minor illnesses: fever or sudden rise in fever, vomiting, drowsiness or apathy. Irritability also may be noted at the onset of meningitis." In spite of the important role assigned to constipation as an early symptom in many textbooks, it has not been common in this series, occurring in less than 10 per cent of cases. "In the older child, headache may be a prominent and helpful early diagnostic symptom." It occurred in 60 per cent of the authors' patients who were at least 4 years old, but was not noted under the age of 3. "A generalized convulsion dated the onset of tuberculous meningitis in about 20 per cent of patients under 2 years old, but was an uncommon symptom after this age and was not noted in children over 5 years old.

"An analysis of 75 cases of tuberculous meningitis not known to be tuberculous before admission to the hospital, revealed that 47 were diagnosed within the first 24 hours. In 10 additional cases the initial diagnosis was brain tumor or brain injury, or poliomyeloencephalitis; 1 infant was at first thought to be mentally deficient because of marked apathy. In almost all cases not diagnosed on admission, meningitis was first suggested by positive tuberculin reactions, subsequent chest roentgen rays and by the results of spinal fluid examinations."

"In most cases the onset of tuberculous meningitis was gradual, the neurological examination remaining normal during the first stage of general symptoms. During the second stage of increasing stupor the neurological signs were at first often transient; hyperactive deep reflexes, diminished abdominal reflexes, positive Kernig and Brudzinski signs and ankle and patellar clonus were frequently noted. Evidence of involvement of the cranial nerves, most often ptosis, strabismus, nystagmus or facial paralysis occasionally appeared during this second stage. Peripheral paralysis and clonic spasms of one or more extremities were sometimes noted as early neurological signs. Fixed or unequal pupils, and irregular respirations of the Biot type were occasionally seen in the second stage, but more commonly in the final or comatose stage of the disease. Some degree of nuchal inflexibility was usually seen early, but a rigidity was often a late sign. The final stage of the disease was usually one of steadily increasing stupor with periods of return to consciousness in rare instances. In the group of cases studied, the duration of tuberculous meningitis from the first symptoms to death varied from 1 to 63 days. Often the three stages of the disease were of about equal length. Occasionally the stage of general symptoms was prolonged. In cases of short duration the neurological signs often appeared at the same time as the general symptoms."

A group of 92 children with primary tuberculosis who developed tuberculous meningitis while under observation gave the authors the opportunity to study the time relationship between the onset of tuberculosis and the first symptoms of meningitis. "Of these, 77 per cent died of meningitis less than a year after the first diagnosis of tuberculosis; over 42 per cent of the cases of meningitis occurred within three months after primary tuberculosis was discovered.

"Therefore, in a child with a manifest primary tuberculosis the physician should look with suspicion on general symptoms whose cause is not obvious, or on symptoms with an apparent good explanation which do not yield to appropriate therapy. Daily fever or sudden rise in fever with no adequate cause should be a danger signal. A convulsion in a tuberculous child, especially in an infant, should always be an indication for an immediate lumbar puncture. Unexplained fever, drowsiness,

and vomiting should suggest the possibility of meningitis in any tuberculous child, regardless of the duration of the disease, when there has been a recent history of a factor which might predispose to tuberculous meningitis: measles or pertussis, a severe fall, a general reaction to a tuberculin test.

"Prompt recognition of tuberculous meningitis will be more difficult when the child is not known to be tuberculous. Early diagnosis will be accomplished in an increasing number of cases, however, if routine Mantoux tests are done in children with fever or general symptoms of unknown origin." In this series of cases, anergy to tuberculin was found to be relatively uncommon even in well developed cases of meningitis, since positive reactions were obtained in at least 85 per cent of the children. A chest roentgen ray may also be of value in diagnosis, since over 90 per cent of the cases of tuberculous meningitis who were not known to be tuberculous before admission to the hospital gave positive evidence of tuberculosis on chest roentgen ray; manifest primary tuberculosis was present in over 75 per cent. "The child who has a convulsion as an initial symptom will only be diagnosed promptly if a lumbar puncture is done. The search for a cause for the convulsion should include a Mantoux test.

"The case of short duration, the fulminating case and the case associated with an incidental infection of obvious origin will present the greatest obstacles to early diagnosis.

"The object of chemotherapy early in the course of the disease is not only to effect a higher percentage of survivals but also to prevent irreversible cerebral changes."

"The spinal fluid of tuberculous meningitis fortunately is often characteristic." A clear fluid with cells ranging in number from 10 to 350 per cu. mm. was found in 86 per cent of the cases; rarely, especially in the fulminating case, the cells may be increased even over 1,000 per cu. mm. In 87 per cent of the cases lymphocytes predominated; the finding of a high proportion of polymorphonuclear leukocytes is usually associated with rapidly progressive cases. "The fluid on standing usually develops a pellicle in which tubercle bacilli can frequently be demonstrated on direct examination. In a few cases, even when the diagnosis is substantiated by autopsy, tubercle bacilli cannot be demonstrated even by culture and guinea pig inoculation. The protein content of the spinal fluid tends to be high and to rise as the disease progresses." In the series of cases studied before the advent of chemotherapy the initial spinal tap showed a fluid with a protein content above average in over 99 per cent of the cases; in over half the cases it exceeded 50 mg. per 100 cc. "The sugar content of the spinal fluid even on the initial tap tends to be low." It was below 38 mg. per 100 cc. in 96 per cent of the cases. "Excluding the finding of tubercle bacilli, the low sugar content is the single most valuable diagnostic finding in the spinal fluid. Next in importance is a progressive decline in the sugar content, even if it remains close to normal." Four children in the original series of cases had a spinal sugar content of over 55 mg. within a week of death. "In general, however, a clear fluid with a moderate pleocytosis, mainly lymphocytes, with a sugar content which tends to be low and a protein content above normal should rouse suspicion of tuberculous meningitis, especially if a pellicle develops on standing."

"Tuberculous meningitis must be considered in differential diagnosis as soon as any child presents evidence of meningeal irritation, even if nothing in the history or examination suggests tuberculosis. Tuberculin test and chest roentgen ray often furnish the first evidence pointing to the tuberculous origin of the meningitis in cases at first considered to be of suppurative or viral origin.

"Actually, once the spinal fluid has been examined, the number of conditions which can be confused with tuberculous meningitis is small. A clear fluid with a moderate pleocytosis is seen in viral infections, such as lymphocytic choriomeningitis. The chemical changes are, however, not marked and the sugar rarely sharply reduced. A fluid typical of tuberculous meningitis may occasionally be seen in chronic influenzal meningitis especially in the presence of a walled-off abscess. However, influenza organisms should be demonstrated on direct examination or certainly by culture within 24 hours. It is unfortunately true that

children with tuberculous meningitis are occasionally treated as cases of influenzal meningitis because a few possible organisms were seen. In such cases, Mantoux tests and chest roentgen rays have been delayed until there is evident failure of response to therapy, and even if the tuberculous meningitis can be arrested, the chance for a complete restitution to normal may have been lost. If a second examination of the spinal fluid within 24 hours shows no definite organisms, in the presence of a rising protein and falling sugar content, a presumptive diagnosis of tuberculous meningitis should be made and treatment started.

"The diagnosis of tuberculous meningitis may be especially difficult in children with miliary tuberculosis who are already receiving streptomycin by the intramuscular route. Such children should be carefully watched for early general symptoms of meningitis, such as somnolence or increased irritability." In 2 cases of miliary tuberculosis who developed meningitis while under streptomycin therapy the sugar content of the cerebrospinal fluid remained normal even after tubercle bacilli could be demonstrated by culture. "An elevated protein content of the spinal fluid in a child with miliary tuberculosis should be checked in 24 hours and, if further increased, should be an indication for treatment even in the absence of a diminished sugar content. In such cases the streptomycin levels of the spinal fluid may be of great value as confirmatory evidence of local inflammatory changes in the meninges. In the absence of meningitis the levels of streptomycin in the spinal fluid are usually not over 3 micrograms per 100 cc. In 2 patients with miliary tuberculosis streptomycin levels of 5 to 40 micrograms were obtained in the spinal fluids before other evidence of tuberculous meningitis was obtained. This masking of the diagnosis of meningitis in miliary tuberculosis because of normal sugar values has stimulated a search for other tests by which early diagnosis of meningitis can be established. The Levinson test and colloidal gold curves may be of value. In children where meningitis was not present, the Levinson test was invariably negative and the colloidal gold curve normal."

In contrast to the child with caseous tuberculous meningitis who in this series invariably died of his disease, tuberculous children may exhibit physical signs and symptoms very suggestive of meningitis and go on to complete recovery. This clinical picture which the authors have called serous tuberculous meningitis is not uncommonly seen on a ward for children with active tuberculosis; it should be considered in the differential diagnosis of tuberculous meningitis preparatory to chemotherapy.

"Serous tuberculous meningitis is probably due to a perifocal reaction around seedings in the early primary or postprimary stage of tuberculosis or to later collateral inflammation around older caseous foci in the cortex or meninges. Such lesions have been demonstrated pathologically in children who died soon after an attack of serous meningitis; in these cases no evidence of tuberculous meningitis was found.

"In the first stages of caseous tuberculous meningitis the differentiation from serous meningitis cannot be made by the clinical picture. Headache, irritability, fever, drowsiness and vomiting are as commonly associated with the onset of serous meningitis as with caseous meningitis. Miliary tuberculosis is frequently associated with either, and its presence therefore does not help in differential diagnosis. The early neurological evidences of caseous meningitis, such as stiff neck, positive Kernig and Brudzinski signs, may also be seen in serous meningitis. Very marked early general symptoms followed by scanty neurological signs should suggest the possibility of serous tuberculous meningitis. Ankle clonus associated only with some degree of stiff neck is the most common neurological sign associated with serous meningitis. Another finding which favors the diagnosis of serous meningitis is roentgen ray evidence of recent local extension of the pulmonary tuberculosis." On the other hand, a convulsion at onset would strongly suggest a tuberculous meningitis, since the authors have no record of a generalized convulsion in a case of serous meningitis, although several children had marked tremor or clonic spasms of the extremities. Involvement of the cranial nerves, except facial paralysis which may be due to tuberculous otitis media, is also not re-

corded in the authors' cases of serous meningitis. "No case of serous meningitis has been really comatose although some were very drowsy. On clinical examination alone it is impossible to distinguish a caseous tuberculous meningitis from a serous tuberculous meningitis. The differential diagnosis may even be difficult in the second stage, but in the third stage of caseous tuberculous meningitis the diagnosis should be obvious on physical examination. However, one cannot afford to delay chemotherapy until the diagnosis is firmly established by the clinical picture.

"The differential diagnosis can be made earlier and more easily by the results of examination of the spinal fluid." While an increase in spinal fluid pressure and in number of cells may be present in either form of meningitis, the authors have found no changes in chemical constituents in serous meningitis; the sugar, protein and chloride content of the spinal fluid remained within normal range. "No pellicle developed in the spinal fluid of a case of serous tuberculous meningitis and no tubercle bacilli were found on direct examination or culture. The finding of a few tubercle bacilli is not incompatible with a diagnosis of serous tuberculous meningitis; in such cases the sugar and protein content of the spinal fluid should be checked daily, since the finding of a few bacilli may be a warning of the possible transition from a serous to a caseous meningitis." The presence of tubercle bacilli in the spinal fluid has been reported by several authors in cases showing no evidence of tuberculous meningitis on postmortem examination. "These authors conclude that 'localized lesions in the central nervous system may be set up by hematogenous infection of a mild sporadic type, not meriting the name of miliary tuberculosis. There is evidence that on such occasions tubercle bacilli may be present, probably temporarily, in the cerebrospinal fluid, that occasionally clinical symptoms and signs may mark the occurrence of this initial infection and that such incidents are not necessarily followed by the development of fatal tuberculous meningitis.' "

"Because of the possibility of subsequent caseous meningitis every patient with serous tuberculous meningitis should be kept under close supervision for several months. Even if the symptoms subside rapidly at least one later examination of the spinal fluid should be made. If follow-up examination of the spinal fluid is done, chemical changes in the spinal fluid indicating a meningitis would be discovered promptly and treatment could be instituted at once." It is the authors' opinion that serous tuberculous meningitis should not be treated by streptomycin, since in the great majority of cases there is spontaneous disappearance of symptoms. "Every effort should be made to protect such children from factors which have been thought to precipitate meningitis. A child who has had serous tuberculous meningitis should not be excessively exposed to sunlight; he should be protected from unnecessary exposure to measles or pertussis; he should not be subjected to tuberculin testing and surgical operations should not be undertaken unless they are essential."

"Once the diagnosis has been established, treatment should be vigorously pursued. The use of streptomycin is definitely indicated in tuberculous meningitis. The physician must, however, decide whether streptomycin should be administered by the intrathecal as well as by the intramuscular route and whether it should be used as the sole therapeutic agent or combined with another tuberculostatic drug. . . . There is no doubt that some cases of tuberculous meningitis can be cured with streptomycin given only by the intramuscular route. However, as the report of the British Medical Research Council clearly demonstrated, the number of cases cured by combined intramuscular and intrathecal therapy is greater than with intramuscular treatment alone." Therefore, since the goal should be the cure of as many cases as possible, the use of intrathecal therapy in addition to intramuscular seems clearly indicated.

"On the Children's Medical Service of Bellevue Hospital, tuberculous meningitis has been treated since December, 1946, with streptomycin combined with a sulfone, promizole."

"Promizole has the disadvantage of acting slowly, and it is inadequate as a sole therapeutic agent in meningitis and in rapidly progressive cases of hematogenous tuberculosis. But it possesses the advantage of ease of administration, since it is given

orally and has relatively slight toxic effects. By the simultaneous use of streptomycin and promizole it was hoped that the child with tuberculous meningitis would benefit from the rapid action of streptomycin; the bacteriostatic effect would be still further enhanced by gradually increasing doses of promizole; after apparent arrest of the disease had been secured, therapy could be continued with the sulfone which can apparently be given safely and effectively for years."

During the treatment of the first cases using combined streptomycin and promizole there was some variation in dosage of streptomycin; the daily intramuscular dose varied from 0.5 to 2.0 Gm. Except for these first cases, the authors have given 1 Gm. of streptomycin daily to all patients regardless of the age or size of the child: in a single dose to well nourished older children; 0.5 Gm. twice daily to infants or emaciated children. "Streptomycin intramuscularly is continued for 180 days. In addition, 0.1 Gm. is given daily by the intrathecal route until toxic symptoms occur or mechanical difficulties arise. If toxic symptoms recur, 0.05 Gm. to 0.1 Gm. is given every second or third day. The course consists of 40 intrathecal injections. If relapse occurs, the full course of streptomycin is repeated by both intramuscular and intrathecal routes.

"Promizole is given orally at six hour intervals. An initial dose of 0.5 to 1.0 Gm. daily is given. In the absence of evidence of toxicity, the dose is gradually increased until a blood level of 1.0 to 3.0 mg. per 100 cc. is obtained; this is the level with which therapeutic results were obtained in the children with miliary tuberculosis. Absorption curves in children taking promizole show that the peak is reached two to four hours after oral administration of the drug. Blood for determination of level should be taken during this period." It is the authors' practice to estimate the blood level on samples of blood taken three hours after promizole has been given. "There is no apparent relation between the level obtained and the dosage or weight of the child. Adequate levels have been obtained with dosage varying from 0.375 Gm. to 8 Gm. daily. It is planned to continue treatment with promizole for three years until the results of treatment can be assessed in a group of at least 25 cases of meningitis."

In cases where promizole has been given in combination with streptomycin relatively few toxic effects have been seen. "It is possible that the evidence of lessened toxicity is due to the small initial doses used and to the gradual increase in the amount of drug given. All children receiving promizole continue to show, at times, a cherry red or pink urine; the significance of this finding is not known. Most of the children have been slightly but not constantly cyanotic. The goitrogenic effect of promizole has been evident in most cases after several months' administration of the drug; the cholesterol content of the blood sometimes becomes elevated and the thyroid gland palpable. In only a few cases has definite enlargement of the thyroid gland been noted; the administration of small amounts of desiccated thyroid apparently counteracts the goitrogenic action of promizole. One girl 6 years old has shown evidence of the stimulating effect of promizole on secondary sex characteristics; after eight months of promizole therapy she showed definite evidence of mammary gland development.

"Toxic reactions of streptomycin have been similar to those reported by all investigators. Vomiting was frequent, especially during the first weeks of administration of the drug; however, in only 1 case was this symptom so severe that therapy had to be temporarily discontinued. Four children had generalized papular or urticarial eruptions, in 2 cases associated with or followed by eosinophilia. In 1 patient the rash developed into exfoliative dermatitis. Only 1 child showed an elevated blood nonprotein nitrogen, associated with cylindruria, and this finding was of brief duration. Four patients became deaf during the course of treatment but in only 2 cases has the deafness persisted after treatment with streptomycin was discontinued. There is, of course, no way of knowing whether the deafness was due to meningitis or to the treatment.

"The most constant toxic result of streptomycin therapy was the effect on the vestibular branch of the eighth nerve. Every patient gave some evidence of ataxia after three to four weeks of treatment. Clinically, every child who recovered made

an apparently satisfactory adjustment; no child has had permanent symptoms of ataxia. Evidence obtained by a simple caloric test (the Kobrak test), however, proved that response to stimulation was invariably lost and sometimes as early as the second week of therapy." Recently 5 early cases were retested, all more than a year after streptomycin had been discontinued. "Four had regained normal response to caloric stimulation as judged by the Kobrak test."

Dihydrostreptomycin has been used in the last 3 cases of meningitis, and loss of response of the vestibular branch of the eighth nerve to caloric stimulation has occurred later than when streptomycin was used. The authors have, as yet, not completed therapy with dihydrostreptomycin in a case of meningitis, but in other forms of tuberculosis treated with dihydrostreptomycin the vestibular response returned within a few weeks after therapy was discontinued.

"Following intrathecal administration of streptomycin, increased vertigo and ataxia, transient strabismus or nystagmus or projectile vomiting may develop within a few hours. Occasionally more serious reactions may occur, chief of which are convulsions, opisthotonos, general muscular rigidity or sudden high fever. Rarely marked drowsiness followed by a prolonged sleep occurs after intrathecal streptomycin. Muscle flaccidity with complete loss of superficial reflexes may be evident for 24 hours or more."

"Since December, 1946, 21 consecutive cases of tuberculous meningitis have been treated; 16 survived. Thirteen of the survivors have completed streptomycin therapy and are continuing with promizole." Discussion of the physical and mental condition of the survivors will be limited to those who have completed streptomycin therapy and hence have been observed for a minimum period of six months; that is, the 13 survivors of the first 18 patients.

"In most cases there was little apparent response to therapy during the first weeks of treatment. Even when streptomycin and promizole were begun during the first stage of general symptoms, the children often developed the neurological picture of the second stage of meningitis and under treatment this phase lasted from two weeks to several months. Even the third or comatose stage of the disease developed under treatment in cases which ultimately recovered." One patient developed meningitis while he was in the hospital under observation for primary tuberculosis. "During the third and fourth weeks of the disease he became blind, then deaf, and led a vegetative existence. By the fourth month of therapy, vision and hearing were restored; there was slow but progressive improvement and on discharge to his home he seemed entirely normal both physically and mentally. Some children seemed to have completely recovered from meningitis even before the six months of streptomycin therapy were completed. Often, however, convalescence was prolonged." One patient showed clinical evidence of tuberculous encephalitis as well as meningitis. "During the third month of treatment she developed difficulty in swallowing and a lagging speech, associated with coarse tremors of the extremities. By the end of six months of streptomycin therapy she was clear mentally but extremely weak and emaciated; after many months of further convalescence she has finally become fully rehabilitated."

Spinal fluid in patients with tuberculous meningitis treated with streptomycin tends to return to normal earlier in children than in adults. "Spinal fluid proteins remained elevated in only 5 patients at the time streptomycin therapy was finished; 2 of these relapsed. Spinal fluid sugar usually returned to normal within a few weeks. Cells showed great variations in numbers but returned to normal in all survivors before streptomycin intramuscularly had been discontinued.

"Of the 13 survivors who have completed treatment, 5 had paralyses of one or more extremities during the first month of meningitis. Neurological weaknesses persist in 4 children; 2 have hemiplegia, 1 child has recovered complete use of his arm but still has a weakness of his leg; 1 child has a residual footdrop. These 4 children are all able to walk; they are improving steadily under orthopedic supervision and physiotherapy. One child developed internal strabismus during the first week of therapy and this condition persisted for six months." Electroencepha-

lograms have been normal except in 3 cases; these show localized changes.

None of the surviving children shows evidence of mental deterioration. "The results of psychometric examinations have been within normal limits."

"Relapses occurred in 3 cases, the only children in whom abnormal electroencephalograms were obtained. In each case the first indication of a return of the meningitis was a change in the chemistry of the cerebrospinal fluid obtained as part of a routine examination during the first weeks after combined therapy was discontinued. The spinal fluid changes, consisting of a lowered sugar and increased protein content, were found 25 to 45 days after the last dose of streptomycin and at the time of diagnosis were not associated with neurological signs. In each case tubercle bacilli fully sensitive to streptomycin were recovered from the first spinal fluid which showed abnormal chemistry values." One patient began to deteriorate physically in the fourth month of his relapse and died shortly thereafter of tuberculous meningitis. "Tubercle bacilli recovered from the spinal fluid just before clinical meningitis developed were resistant to more than 100 micrograms of streptomycin." One patient after finishing his second six month course of therapy relapsed a second time, again about six weeks after streptomycin was discontinued and diagnosed only on spinal fluid findings. "Tubercle bacilli cultured from his spinal fluid at the time of his second relapse were again fully sensitive to streptomycin. This boy has just completed his third six month course of treatment with streptomycin and is in good general condition."

Report of 10 Cases of Poliomyelitis in Infants Under 6 Months of Age— MOUTON, CHARLES M., SMILLIE, JOHN G. AND BOWER, ALBERT G. — *Journal of Pediatrics*, 36: 482 (April) 1950.

Poliomyelitis seems to spare the infant under 6 months of age. Only 17 cases in infants under 6 months of age have been reported in the literature since 1897.

"In the poliomyelitis epidemic of 1948 in the county of Los Angeles there were 2,973 cases seen in the Communicable Disease Unit of the Los Angeles County Hospital and only 10 of these patients were under 6 months of age."

"These 10 infants were admitted to the hospital between August and December, 1948. The youngest was 14 days of age and the oldest 5 ½ months. Four were under 3 weeks of age and 8 were under 2 months. Eight of the 10 were males. All those 2 months of age or younger were males. All were Caucasian. Nine were of the spinal type. Only 1 patient had bulbar signs. The mortality for the group was 10 per cent. This 1 death occurred in a 5 ½ month old girl who was admitted on September 17 with a three day history of fever, irritability, anorexia, weakness, and paralysis of the lower extremities. On the twentieth hospital day bronchopneumonia developed. Death intervened on October 16, 1948, the twenty-sixth hospital day.

"An attempt was made to ferret out any possible contact with the disease in each case. However, only 2 of the 10 patients had known contact. One infant, 14 days of age, developed symptoms five days after his mother manifested the disease. The second infant, 3 weeks of age, developed poliomyelitis 10 days after the onset of infection in his 5 year old brother. The remaining 8 infants had parents and siblings who were clinically well in every respect."

Two of the patients had an upper respiratory infection, 2 had manifested irritability, 5 of them had fever over 101° F., 5 had been anorexic, and in 8 of the infants weakness or paralysis had been noted prior to admission. "Two of the 10 infants had weakness and paralysis as the only findings. Conspicuous by their absence were: meningeal signs, convulsions, and gastrointestinal disturbances. There was a minimum of extension of the disease process after hospitalization."

"The highest white blood count was 26,000 and the lowest 5,250, the average 11,000. The neutrophil count varied between 36 per cent and 72 per cent. Spinal cell counts presented a low of 8 lymphocytes and a high of 330 (all lymphocytes). Two had 100 cells or more.

"Treatment was essentially supportive. All received hot moist packs. Intramuscular penicillin was given to 7 as a prophylaxis against secondary infection.

"Neurological examination of the 10 patients revealed that 7 had absence of deep reflexes, 1 had right peripheral facial paralysis, 1 had absent gag reflex, and 1 was unable to swallow. Six had intercostal weakness and 2 diaphragmatic, yet only 1 of these patients required the respirator. When discharged from the hospital, residual involvement was as follows: 5 patients had paralysis of one extremity or more (right leg in 2, right arm in 1, left arm in 2, both arms in 1, and both legs in 2); 1 patient had generalized muscle tenderness as the only involvement; 1 patient had scoliosis. Eight of them had some paresis, either with or without paralysis."

Aureomycin in the Treatment of Resistant Bacilluria — LoPresti, Joseph M., Ross, Sidney and Rubin, Milton B. — *Pediatrics*, 5: 734 (April) 1950.

Ten cases of urinary tract infections in children have been treated with aureomycin during the past few months at the writers' hospital. "Of these, 4 were males and 6 females. Three patients were under 4 years of age while the others ranged from 4 to 8 years.

"All these patients showed pyuria and most of them had symptoms referable to the urinary tract; e.g., dysuria, frequency, incontinence, enuresis and flank or lower abdominal tenderness. Nine of the patients received previous therapy without effect. The preceding therapeutic agents included mandelic acid, penicillin, sulfadiazine, and streptomycin.

"In 8 patients, the etiologic agent was *Esch. coli*, while the other 2 cases had mixed infections with *Esch. coli* and *Staph. aureus*." Sensitivity studies against *Esch. coli* were carried out in 8 of the 10 cases and in no instance was the organism found to be resistant to more than 1 μgm./cc. of aureomycin.

"All the children treated in this series received aureomycin orally in a dosage of 30 to 60 mg./Kg. body weight/24 hours in a four hour divided dosage schedule. When the child was unable to swallow an intact capsule, the drug was offered in chocolate syrup or syrup of cherry. No attempt was made to vary the *p*H of the urine; diet and fluids were permitted as desired. The duration of therapy varied from four to eight days. Daily urinalyses and several urine cultures were done during therapy. Intravenous pyelography was carried out in 5 patients; in 4 instances there was no demonstrable uropathy while in the remaining patient a bladder neck obstruction was observed.

"Urine cultures in 9 of the 10 patients became sterile within 48 hours while the remaining 1 became negative in 4 days. In 5 patients, pyuria had disappeared by the end of the second day of therapy; the remaining patients showed no pyuria after four days of treatment. The subsidence of symptoms corresponded to the disappearance of the pyuria. At the onset of aureomycin therapy, fever was present in 2 children. The temperature in both cases returned to normal within 24 hours after treatment was instituted. The more dramatic of these was a Negro girl 2 years of age who had temperature elevations between 37.2 and 40° C. for 21 days prior to therapy. The temperature returned to normal 24 hours after aureomycin was started and the patient remained afebrile thereafter.

"There have been 3 relapses in this series. One of these was in a Negro boy 8 years of age who had an associated anomalous bladder neck obstruction." The most important single factor in the efficacy of any treatment of urinary tract infections is the presence or absence of complications. "Other pathologic conditions, such as anomalies, tumors, stones, residual urine or foreign bodies, must be cared for, before the infection can be eradicated. Cultural reversals in the other 2 cases occurred in children who received aureomycin for a period of only four days. In these 2 instances, it was felt in retrospect that therapy was probably of insufficient duration. Attempts to get either of these 2 children back into the hospital for retreatment were unsuccessful."

Five patients developed vomiting during the course of aureomycin. "This symptom occurred primarily in the older children and usually manifested itself within 24 hours after institution of therapy. As a rule, it did not occur concomitantly with administration of the drug but most often during or just after a meal. Vomiting ceased when treatment was discontinued."

Aureomycin Treatment of Pertussis — CHANG, SHIH-MAN, WELLS, EDWARD BUIST, PLACE, EDWIN H. AND FINLAND, MAXWELL — *Journal of Pediatrics*, 36: 443 (April) 1950.

"Aureomycin was used orally in the treatment of 22 hospitalized patients with pertussis and the clinical and bacteriologic findings in these patients were compared with those in a similar number of comparable and contemporary patients treated under the same conditions without any antibacterial therapy." The patients were all observed on the same ward during the four months, August through November, 1949. "All had clinical findings consistent with pertussis but they were admitted to the series only after *Hemophilus pertussis* was identified in their nasopharyngeal culture."

"The two groups were quite comparable with respect to the age distribution. (Approximately 80 per cent were under 3 years.) Among the aureomycin-treated patients, 6 had received pertussis immunization prior to the onset of this illness, 2 of them had been incompletely immunized within two months, and the other 4 had been vaccinated more than one and one-half years previously. Among those who received no antibiotic therapy, a definite history of pertussis immunization was elicited in 4 patients while in 4 others the history of such immunization was not known. The average duration of symptoms at the time of admission to the hospital was about the same in the two groups (8.8 days for the aureomycin-treated group and 9.5 days for the other group), but the delay in beginning aureomycin administration ranged from one to eight days and averaged almost four days. Other features such as number and severity of paroxysms and occurrence of leukocytosis during the first three or four days in the hospital were also very similar in both groups of patients."

"The dose of aureomycin used in the first 10 patients was about 100 mg. of the crystalline hydrochloride per Kg. body weight per day, and subsequent patients were given 60 mg. per Kg. per day. Treatment with aureomycin was continued for a total of five days in the first 10 patients and because of inadequate bacteriologic and clinical responses in 3 of these 10 patients, subsequent patients were treated for 10 days. Two of the 3 patients who relapsed were given a second course of aureomycin for five days. The daily amount was divided into four equal doses and was given during feedings, the contents of the capsules being mixed with applesauce or some other acceptable vehicle or incorporated in a small portion of the formula which was given first and then promptly followed by the remainder of the formula. If vomiting occurred less than an hour after a dose, the same dose was promptly repeated. The patients who did not receive aureomycin were not given any antimicrobial agents except for the treatment of complications, and no antiserums were used in any of the patients."

The last positive cultures in the 3 patients who had clinical and bacteriologic relapses were obtained on the twenty-first, twenty-third, and fourteenth hospital days. "In all the other patients who were treated with aureomycin all the cultures taken after the third day of therapy were negative for *H. pertussis*. Among the 22 patients who did not receive aureomycin, there were 12 who had positive cultures on or after the seventh day in the hospital and 7 had positive cultures on or after the fourteenth hospital day. The last positive culture in all the patients who did not receive aureomycin was obtained on an average of nine days after admission."

"Effect on Cough.—The frequency and intensity of the paroxysmal cough began to decrease after the second or third day of aureomycin therapy and, in most of the aureomycin-treated patients this decrease in symptoms continued steadily until the cough subsided completely and the patients were discharged. In 3 of the 10 patients who received aureomycin for only five days there was a relapse in symptoms within the first few days after the antibiotic treatment was stopped and in 2 of these 3 patients the paroxysms were again brought under control after a second course of aureomycin given for five days. Among the 12 patients who were treated with aureomycin for 10 days, 2 had an increase in cough for several days after apparent improvement. Most of the patients who did not receive any aureomycin had little or no change in the cough, which continued

with the same intensity and in some patients even became aggravated during the first two weeks in the hospital and then gradually began to improve."

Duration of Cough.—"The average duration of the paroxysmal cough in the hospital was about eight and one-half days shorter among the patients who were treated with aureomycin than in those who were not so treated. The total duration of the paroxysms in the latter cases was 30.3 days after admission to the hospital while in those treated with aureomycin the paroxysms continued for an average of 21.7 days after admission or 18 days after the first dose of aureomycin."

Frequency of Paroxysms.—"For the patients who received aureomycin the average number of paroxysms dropped sharply and steadily from the seventh to the fourteenth day, leveled off for the next five days, and then continued downward more slowly." The level portion was due to the 5 patients who relapsed following therapy. "By contrast, the first drop in the average number of paroxysms per day among the patients who were not given aureomycin occurred on the seventeenth hospital day and the decline then continued steadily.

"Cough Index.—In order to assess the severity as well as the frequency of paroxysms, a 'cough index' was established. For this purpose the following arbitrary ratings were assigned to each paroxysm according to the severity, as recorded by the attending nurses: severe—4; moderate—2; and mild—1. The total of these values for each day was termed the cough index." When the average daily cough indexes for the 22 aureomycin-treated patients and the group of patients who did not receive aureomycin were charted the two curves were very similar to those representing the number of paroxysms in the two groups except for the more precipitate character of the initial drop in the cough index curve representing the aureomycin-treated patients.

"Leukocyte Counts.—There did not appear to be any correlation between the total or differential blood counts and the progress or severity of the disease in the present cases. This was true both among those treated with aureomycin and in those from whom this antibiotic was withheld. After the second hospital week, however, the total counts were significantly lower in the aureomycin-treated cases.

"Mortality and Complications.—There were no fatalities in either group. Only one complication; namely, otitis media, occurred in 1 of the patients who did not receive aureomycin, and this was the only patient in both groups who had any significant fever."

"Toxicity.—There were 6 patients who had loose bowel movements and some vomiting unrelated to paroxysmal coughing during the period of aureomycin treatment. In no instance was this severe enough to warrant discontinuing the therapy. There were no other toxic effects of aureomycin noted in any of the patients."

Staphylococcus Aureus in an Outbreak of Infantile Diarrhea — LYON, HARVEY B., JR. AND RANTZ, LOWELL A. — *Pediatrics*, 5: 617 (April) 1950.

An outbreak of infantile diarrhea occurred suddenly in the Stanford University Hospital Nursery which consists of four separate rooms for full term newborn infants and one large room for premature infants. "This incident was limited to two of the full term nurseries."

"The first loose stools appeared at about the same time in 2 infants in Room No. 1. Bilateral conjunctivitis appeared shortly after birth in 1 of these infants. A bacterial etiology of this disease was not established since only a few *Staph. aureus albus* were recovered from the discharge. Both of these infants were dismissed without stool cultures or medication but it is known that diarrhea did not continue at home. The third infant to be affected in this room entered during the early phase of the epidemic and was the last to develop signs of infection, about 24 hours after the others.

"Nine out of 10 newborn infants in Room No. 2 developed loose stools within a 10 hour period. The only exception entered the room 4 hours before the first diarrheal stool was noted and did not receive anything by mouth until 12 hours after entry. A water feeding was then given. Two hours later this infant was transferred to an observation room. The most recent dismissal prior to the outbreak was four hours before its onset. This child

had a formula feeding two hours before leaving the hospital and remained well. Thus the contamination causing the epidemic might have occurred during the feeding following dismissal of this child.

"Manifestations of the disease were limited to loose, greenish stools occurring 4 to 10 times a day and persisting over periods of from 30 to 84 hours. No vomiting or fever developed and no signs of dehydration were noted. Close observation of the skin, ears, nose, throat and lungs revealed no signs of infection at any time.

"Isolation precautions were instituted shortly after the first diarrheal stools appeared. One doctor and one nurse were assigned to the rooms involved and aseptic technic was carefully practiced.

"*Staph. aureus* was recovered in large numbers from stools obtained from 7 of the 9 patients and cultured directly on blood agar plates at the onset of diarrhea. The organism in every instance formed coagulase. One of two specimens devoid of staphylococci contained a heavy growth of *P. vulgaris* which may have interfered with the growth or isolation of any staphylococci present; in the other case there was a heavy growth of nonhemolytic enterococci. Throat cultures of 1 of the infants whose stool contained a heavy growth of staphylococci revealed many of the same organisms. This organism was not isolated from the nasopharynges of the other 8 infants.

"Dietary treatment was started after the initial cultures had been obtained. Water was given by mouth every three hours for the first eight hours. An oral amigen-electrolyte mixture was then administered for a 28 hour period and was followed by a Dryco formula without sugar.

"Chemotherapy was begun when the bacteriologic findings were reported. Four of the infants had been dismissed from the nursery during the preceding 24 hours and thus were not treated with antibacterial agents. Seven of the remaining 8 infants received dihydrostreptomycin in a dosage of 0.1 Gm. every four hours mixed in bottle feedings. One infant received sulfasuxidine 1.0 Gm. every four hours in the same way.

"Eight stools were cultured two hours after starting medication. No staphylococci were isolated from 6. Two, obtained from infants who were receiving dihydrostreptomycin, showed a light growth of this organism. On the next day, after 26 hours of medication, 1 of 7 stool cultures was positive for *Staph. aureus*. This patient was the 1 receiving sulfasuxidine. He was dismissed on the same day without further cultures or treatment, but no diarrhea was reported at home. All 7 throat cultures were negative at this time. Five patients remained in the hospital on the fifth day. All cultures were negative for staphylococci and all stools were normal in appearance. None of the patients exhibited diarrhea after leaving the hospital according to reports from attending physicians.

"The nursery staff was studied for the purpose of discovering a possible source of the epidemic. Evidence of infection by staphylococci was not obtained in any of the personnel, nor were these organisms isolated from the materials obtained from the nose and throat of the four nurses who were immediately responsible for the care of the infants before the outbreak began."

Typhoid Fever in 14 Children Treated with Chloramphenicol — Reilly, William A. and Harrel, J. A., Jr. *Journal of Pediatrics*, 36: 440 (April) 1950.

From March, 1949, until October 1, 1949, the authors have treated a total of 9 children with chloramphenicol (Chloromycetin), all of whom showed rapid response to the drug. All of the cases were proved by suspicious clinical course, positive blood, stool, and urine cultures, and by diagnostic blood agglutinin titers.

The ages of the patients varied from 2½ to 13 years; there were 6 girls and 3 boys, 7 of whom were white and 2 Negro. "Two of the patients had a history of previous immunization for typhoid within the previous year."

"The treatment was begun from 8 to 34 days (average, 15 ¼ days) after onset of disease." All of the patients were treated with initial dosage of 50 mg. per Kg. of the body weight followed by 125 mg. irrespective of weight every two to three hours in the smaller children, and 250 mg. every two to three hours in the larger children for approximately six days; then the dosage was given every four to six

hours. "The total dosage varied from 8 Gm. to 29 Gm. with total dosage averaging 13 Gm. The oral ingestion of the drug was not difficult. It can be given rectally in a 25 to 50 per cent greater dose; the capsule tip can be perforated for ease and quickness of absorption. Suppositories will be available. It can be used intravenously as a 10 per cent propylene glycol solution.

"The number of hours before the patient was fever free varied from 48 to 96 hours, with a rough average of 72 hours."

Between March and October, 1949, the drug was not withdrawn until there was a period of from four to five days of normal temperature (a total of seven to nine days of such therapy). Since mid-September, the drug has been given for 8 to 14 days to 2 of the 9 patients to prevent relapse.

"There were no drug reactions, disease complications, sequelae, or known carriers."

The Lungs in Measles — Sédallian, P., Maral, P., De l'Hermuzière and Traeger — *Pediatrie*, 39: 112, 1950.

The authors studied the roentgenologic aspects of the lungs in measles serially in all admissions. In 1929 a fundamental report was published on this subject and the authors confirmed their conclusions that hilar pictures with accentuation of the pulmonary markings, pneumonic parenchymatous pictures and pictures of interlobar inflammation are extremely frequent, appear very early during the preeruptive stage and persist long after clinical cure, usually without being suspected clinically, while rarely normal pulmonary findings are encountered.

The authors' material included 71 cases; 46 patients were below the age of 5, 12 were between the ages of 5 and 10, 4 were between the ages of 10 and 15 and 9 were older than 15. Most patients were hospitalized during the frank eruptive stage, but some were not admitted until slightly later. The first pictures were thus taken between the first and fifth day after onset of the eruption, and in the majority of cases the course was followed up until the fifteenth to twentieth day.

In order to avoid any confusion with tuberculous pictures cutireactions were done in all cases until discharge and were found negative except in 3 cases. Isolated hilar pictures with tramitis were found in 37 cases, normal pictures in 13, parenchymatous pictures in 11, pleural in 5, miliary in 2, bullous emphysematous ones in 2 and atelectasis in 1 case. Isolated hilar enlargement with accentuation of the markings thus is the most frequent isolated finding, and is also found associated with the parenchymatous and pleural pictures. The hilar picture usually did not show the polycyclic shadows encountered in tuberculosis but rather showed a mass with soft contours from which tracts radiate into the parenchyma of both lung fields, particularly towards the base and the diaphragmatic cupola; these were termed cardiophrenic shadows.

The accentuation of the pulmonary markings varies in intensity and may assume a reticular and granite-like miliary tuberculosis; in 1 of the authors' cases diagnosis was difficult particularly as an enlarged spleen was present, but the elements of these pseudomiliary pictures are larger and thicker than those of true miliary tuberculosis. The tramitis is usually particularly marked near the hilar region. The glandular pictures correspond anatomically to hypertrophy of the glandular groups in front, below and behind the trachea, while the tramitis is attributed to peribronchial inflammation, as found on autopsies after death early in the course of the disease. This combination of glands and tramitis is found whether the measles are benign or complicated; if it is isolated, usually no clinical signs are demonstrable, and among 37 cases the authors found no clinical or functional signs in 30, while 4 showed very discrete rales and 3 slight dyspnea. The glandular hypertrophy is benign in the majority of cases but may cause complications as found by the authors in the case of a child, aged 20 months, who developed total atelectasis of the right lung on the eighth day of measles; bronchoscopy demonstrated bronchial compression and tomographies showed the hypertrophied glands. In the 2 cases with bullous emphysematous pictures no bronchoscopic or tomographic verification was done. One of the five pleural pictures involved a purulent pleurisy as complication of pneumonia, while the other four represented banal

interlobar inflammation in front of the hypertrophied glands. The fissural involvement did not produce any clinical signs; several writers found it much more frequently; namely, in 26.2 per cent of their cases as compared to the authors' 5.6 per cent. Thickening of the axillary pleura has been considered frequent but did not occur in the authors' material. The parenchymatous pictures included three of typical pneumonia with homogeneous opacity of an entire lobe, four of bronchopneumonia involving both lung fields but little marked at the apexes, three of pulmonary congestion with an opacity with ill delimited contours particularly at the base, and finally one picture of a right paratracheal shadow which because of intensity and shape indicated pneumonic infiltration rather than enlarged glands; in this last case the cutireaction was positive, however. Parenchymatous involvement was always associated with a hilar ganglionic reaction. Definite pulmonary clinical signs showed in 9 of the 11 patients, while 1 pneumonic picture and 1 congestive one were clinically silent. Parenchymatous pictures were found by several writers in 52 per cent of their cases but they took their pictures at an earlier stage.

The hilar pictures appeared on the first day of the eruption in 4, on the second and third day in 7 cases each, and on the fourth and fifth day in 9 cases. In 17 cases they were still demonstrable after the tenth day; 1 miliary picture could be followed for two months when the reticular aspect diminished markedly while the hilar glands remained hypertrophic. Three of the four fissural pictures appeared during the first three days. The bullous pictures were still demonstrable after three weeks. Only the parenchymatous pictures showed a more rapid course, with dissociation between the picture of infiltration and the associated hilar picture, the latter persisting much longer than the former.

Age seems to have an influence on the frequency of the appearance of the pictures described, in that the lungs of children below the age of 5 react earlier and stronger to the measles; the normal pictures were encountered in the older patients.

Symposium Section

Deoxycortone and Vitamin C in Rheumatoid Arthritis

It would seem incredible that such a mass of literature on the hormone treatment of rheumatic conditions should have accumulated within one year following the preliminary report of Hench, Kendall and their associates[1] of their encouraging successes with cortisone and ACTH were it not for certain trends which are sometimes not easy to comprehend.

Shortly after the publication of this report we reviewed it in this section[2] together with the reactions of an especially prominent group who heard Dr. Hench and Dr. Kendall speak before the Seventh International Congress on Rheumatic Diseases which met in New York City in the early part of June of 1949. It seemed to us that it was most fortunate that this representative group from many parts of the world should have convened in this country so shortly after the studies of Hench and Kendall had reached a stage when they were ready to present their progress for critical consideration. They not only were able to report the impressive results which they had obtained in a small series of patients who were benefited by the study which they have consistently maintained, since their first announcement, is "an investigative procedure, not a treatment," but they had the satisfaction of knowing that their preliminary clinical observations had been corroborated by a selected number of colleagues with whom they had shared the then very scarce and expensive cortisone and ACTH. This was made possible, according to Hench and Kendall and their associates, by the cooperation of Doctors Randolph Major, vice president, and James M. Carlisle, medical director, of Merck and Company, Inc. and Doctors Jacob van de Kamp and Lewis H. Sarett of the Merck Research Laboratories, all of whom participated in the development and production of cortisone, and by Dr. John R. Mote,* director of medical research of Armour and Company, who supplied ACTH. Later Doctors E. Gifford Upjohn and H. F. Hailman of the Upjohn Company supplied compound F (17-hydroxycorticosterone) for further investigations.

Among those to whom small amounts of the new compounds were made available so that they, too, were able to report results at the Congress, were Dr. W. Paul Holbrook of Tucson, Arizona, president of the Arthritis and Rheumatism Foundation; Dr. Walter Bauer of Harvard Medical School; Dr. Richard H. Freyberg of Cornell University Medical School; Dr. Edward Rosenberg of Michael Reese Hospital, president of the American Rheumatism Association, and Dr. Edward Boland of University of California Medical School.† The observations of this representative group were discussed in our first review and amplified in our second.[3] Suffice it to say here that the consensus at the International Congress, as gathered from subsequent reports in American and foreign articles, is that "it was a wonderful thing to hear and see (in still and moving pictures) the effects produced in a few hours in apparently completely crippled patients."

1. Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis, *Proc. Staff Meet., Mayo Clin.*, **24**:181 (April 13) 1949; Hench, P. S., Slocumb, C. H., Barnes, A. H., Smith, H. L., Polley, H. F. and Kendall, E. C.: The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, *ibid.*, **24**:277 (May 25) 1949; Kendall, E. C.: Some Observations on the Hormone of the Adrenal Cortex Designated Compound E, *ibid.*, **24**:298 (May 25) 1949. Extensive bibliography appended to each of these articles.

2. Editorial: Adrenal and Pituitary Hormones in Rheumatic Diseases, *Internat. M. Digest*, **55**:116 (August) 1949.

*The Proceedings of the Conference on ACTH sponsored by Armour and Company, Chicago, October 21 and 22, 1949 is now in the process of being published. These proceedings will be edited by Dr. Mote and will contain contributions by an authoritative group.

†A contribution by this group will appear in the Proceedings of the Seventh International Congress on Rheumatic Diseases, New York, May 31, 1949 now in the process of publication.

3. Editorial: Cortisone, ACTH and Deoxycortone Therapy, *Internat. M. Digest*, **56**:301 (May) 1950.

So, following the International Congress on Rheumatic Diseases, a well chosen team of investigators came into existence to continue the study of what Hench and Kendall have clearly contended is "an investigative procedure, not a treatment" and what Dr. Tom Spies of Northwestern University has called "a tool of clinical and laboratory research" in referring to ACTH in the study of which he was one of the pioneers. All of the members of the early teams, as well as many others like Spies who joined with them soon after the problem was launched at the Congress meeting, were in full agreement that Hench and Kendall's contribution was just what they contended it was—a physiologic approach to the problem of rheumatic conditions. They felt that an important milestone had been reached, after about two decades of work, by these two investigators. As has been emphasized in our two previous reviews,[2,3] it should be recalled that Kendall gave us thyroxine in 1914 and, later, glutathione from the same laboratory from which he released the hormone from the suprarenal cortex, and that Hench had been studying the pathologic physiology of rheumatic diseases since 1929. It is not surprising that together they should be physiologically minded and visualize a biochemical approach to the control of the rheumatic diseases which have yielded to no other.

There was likewise full agreement that there were many problems to be solved before a "treatment" could emerge from what Hench and Kendall still consider "an investigative procedure." The first in importance was the availability of the hormones without which there could be little progress. Production was clearly a herculean task. Those who accepted it, especially Merck and Company, made it perfectly clear at the outset that large supplies could not be expected very soon. Nevertheless, some encouraging progress has been made by the Merck group, Armour and Company and the Upjohn Company toward reducing the steps necessary. But it has been difficult to reconcile the number of case reports with the available supply.

It was also agreed that before any supply that might become available should be released for general use, much more would have to be learned about how these hormones acted, their dosage, toxicity and the many other criteria by which any new drug is judged before it is used on human subjects.†† Obviously it was realized that this would take time and as a consequence suffering patients, doctors and drug houses who expected eventually to distribute perfected materials would have to exercise the greatest amount of forbearance and cooperate toward an orderly study of what now appears to be a problem which has more ramifications than any which has risen in many years. This emphasized the importance of allotting the available material to centers in which the research staffs were fully competent to collaborate and contribute to the increasing number of phases of the problem as a whole. It is quite clear that this has been done by the original teams and, as has been mentioned, there has been an astonishing amount of literature within about a year after Hench and Kendall awakened interest in the very costly adrenocortical extracts which have been studied sporadically over the past 20 years. Among earlier diseases studied were pemphigus, Addison's disease, vomiting of pregnancy and disturbances of neuromuscular function. To these have been added many more.

It has been difficult to follow and interpret the significance of the many able contributions for the very simple reason that most of them are offered as nothing more than preliminary progress reports based on limited experience. They do, however, forecast that we may be on the threshold of revolutionary changes in the management of many diseases entirely unrelated to rheumatic conditions. So when we previously suggested that one or another of the hormones had been tried on diseases ranging from asthma to dementia praecox, we were not facetious. Already lists are being compiled from the vast number of contributions in which diseases are tabulated under such headings as useful, may be useful, questionable value, no value and detrimental. Obviously the physician practicing medicine is confused. His patients

††The Special Feature article of 121 pages by Hench, Kendall and associates which appeared in *Archives of Internal Medicine* [**85**: 545-666 (April) 1950] and their preceding article which appeared in the same journal [**85**: 199-258 (February) 1950] should be on the reading list of all seeking authentic information on all these criteria. See page 6 for brief abstract of the first of these.

are demanding that he treat them with these hormones about which they are reading in the papers and magazines, hearing, and seeing in the national pictorial weeklies. It is not enough for them when he says that the real material is not available for general use, that there must be years for investigation, that there are ill effects and all the other alibis his ingenuity suggests. He is further aggravated by advertising letters and multicolored sheets extolling the virtues by quoting favorable parts of articles and letters from doctors who have used the particular substitute extract offered in the treatment of rheumatic conditions. It is not necessary to be any more specific because we are certain that practically every doctor who reads this has received the advertising matter which we have before us as this is written. There is one part of it which impresses us and that is the admonishment, which several emphasize, to lay in a supply of this "hard to get" material. Some "respectfully" suggest the amount.

* * *

But we started out to discuss deoxycortone and vitamin C in rheumatoid arthritis. However, we felt that the foregoing prologue might illustrate why this adrenocortical preparation was utilized to appease the demand for action pending the development of cortisone or ACTH to a stage where the more conscientious thought they should be released for general use and—of course—when adequate supplies were available. In fact we have seen it written "to by-pass" and "to supersede" cortisone and ACTH in arthritis.

It seems that in 1942, two Swedish workers showed that the implantation of calf hypophysis in a case of severe rheumatoid arthritis caused the disease to take a more favorable course. So when the work of Hench and Kendall with cortisone derived from the adrenal cortex and ACTH derived from the hypophysis was given worldwide acclaim, Lewin and Wassén[4] of Sahlgren's Hospital in Gothenburg, Sweden, considered that some material similar to that which Hench and Kendall used in rheumatoid arthritis might likewise be beneficial in the same condition. Lewin selected deoxycortone (desoxycorticosterone) acetate in 1 ml. of oleum arachis, immediately followed by an intravenous injection of 1 Gm. of ascorbic acid (10 ml. of 10 per cent solution).

Following this they contend that within "five minutes after the injections the articular pain began to diminish and the articular mobility began to increase. Fifteen to 30 minutes later the pain had practically disappeared and the mobility improved as much as the anatomical changes in the joints and muscular atrophy would allow. All the patients reacted in a similar way. In some cases the improvement was astounding. One of the patients was completely crippled by pain and contractures after rheumatoid arthritis for 15 years: after *one* combined injection, she sat up with ease and moved her arms and legs about freely; all her pain had gone. It was noted that the skin became warmer and redder in the articular region after the injection. Some patients became greatly exhilarated after the injections—more than one would expect from the mere relief of pain.

"The effect lasted from 2 to 6 hours, occasionally more than 24 hours. It seems as though it lasts longer with each further injection. In more acute cases one or two injections have been enough to vanish the pain for two or three weeks."

Attention is especially invited to the fact that we have quoted the results directly from the original preliminary communication of Lewin and Wassén. It is understandable how they caused enthusiasm which in some was not far removed from hysteria. Naturally drug houses lost no time in marketing deoxycortone and ascorbic acid which were, apparently, more conveniently available than cortisone and ACTH which it was believed could be "by-passed" and/or "superseded." In any event, it was advertised by its original name and by rapidly evolved trade names. Apparently, these remedies were first placed on sale by many companies in England. This was probably due to the traditional prevalence of rheumatic conditions in the British Isles.

Letters appeared in British journals, especially the *Lancet*, from physicians re-

4. Lewin, E. and Wassén, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis,' *Lancet*, **2**:993 (November 26) 1949. (This appeared in the section of the *Lancet* headed "Preliminary Communication.")

porting results similar to those of Lewin and Wassén. These letters appeared each week in most of the issues from about December of 1949 on through the early months of 1950. In each instance, with one or two exceptions, the reported results were in single cases but taken as a whole they were impressive. Follow-up letters were not written. A report by Leif Hallberg,[5] a countryman of Lewin and Wassén and an assistant physician at the county hospital in Örnsköldsvik, Sweden, in the *Lancet* suggested that deoxycortone and vitamin C effected results that were even more dramatic than cortisone. However, five other papers in the *Lancet*, in the latter part of 1949, report no benefits with the same treatment. Two of these are by Spies and his associates.[6]

What now appears to be a definite turn against deoxycortone and vitamin C in Great Britain is reflected in the report of a more carefully controlled study from the Glasgow Royal Infirmary by Currie and Will. These authors express regret that the favorable reports have been based on uncontrolled experiments and that improvement alone has sometimes been accepted as evidence of improvement in the joints. However, we have reprinted this article elsewhere in this issue* for the benefit of those who have been curious about this material which has been so widely exploited in England and later in America. It would seem that the conclusions of these authors should offset some of the rather incomprehensible criticism of cortisone and ACTH, which those who are participating in what Hench and Kendall consistently contend is nothing more than "an investigative procedure, not a treatment."

* * *

Further in support of the conclusions of Currie and Will of Glasgow Royal Infirmary comes the report of Bywaters, Dixon and Wild,[7] who headed a Special Unit for the study and care of Juvenile Rheumatism from the Department of Medicine, Postgraduate Medical School of London. This group followed 10 patients rigidly and statistically analyzed their responses because they had failed to observe any obvious bedside improvement following the technic of Lewin and Wassén, despite the numerous claims of their own countrymen and others. The criteria for the selection and study of the 10 patients were all that was necessary to justify their conclusions that "from limited but intensive experience—and in common with Kellgren (1949), Spies et al. (1949), Hart and Starer (1949), Fletcher et al. (1950), Hartfall and Harris (1949), Kersley et al. (1950) and Currie and Will (1950)—— deoxycortone and ascorbic acid *has no measurable or appreciable effect on rheumatoid arthritis* beyond that which follows any nonspecific injection or treatment, and that it is not in any way comparable to ACTH." "While it is a thankless and even dangerous task," they continue, "to try to account for other investigators' results, we might perhaps suggest that the substitution of the drug to be tested in place of preliminary saline injections, unknown to the patient, and if possible also to the nurse, is an essential requirement of a careful study." To this they add, "The path of therapeutic advance *is strewn with the bones and bottles* of those who have neglected such precautions."

Small wonder then that the *Lancet* should follow a week later with an editorial[8] which leaves little doubt of their opinion concerning deoxycortone—and they include pregnenolone—in rheumatism. They open their comment by calling attention to the fact that the treatment of rheumatoid arthritis with deoxycortone and ascorbic acid was widely repeated and at first the favorable reports were as numerous as the unfavorable. This doubtless refers to the letters printed in their "Letters to the Editor" section to which we have referred in this and our other editorial reviews.[2, 3] Then they refer to the certain fact that many physicians had no

5. Hallberg, Leif: Effects of Deoxycortone and Methylene-Blue in Rheumatoid Arthritis, *Lancet*, **1**:351 (February 25) 1950.
6. Spies, T. D., Stone, R. E., de Maeyer, Edouard and Niedermeier, W.: Deoxycortone with Ascorbic Acid Versus Adrenocorticotropic Hormone in Rheumatoid Arthritis, *Lancet*, **2**:1219 (December 31) 1949; Spies, T. D. and Stone, R. E.: Pituitary Adrenocorticotropic Hormone (ACTH) as a Tool of Clinical and Laboratory Research, *Lancet*, **1**:11 (January 7) 1950.
7. Bywaters, E. G. L., Dixon, A. St. J. and Wild, J. B.: Deoxycortone and Ascorbic Acid in Treatment of Rheumatoid Arthritis, *Lancet*, **1**:951 (May 20) 1950.
8. Editorial: Deoxycortone and Pregnenolone in Rheumatism, *Lancet*, **1**:1003 (May 27) 1950.

* See page 3.

success with the method but were reluctant to present negative findings because such action, the *Lancet* contends "is always an ungrateful task." "The view of the large majority," says the *Lancet*, "is that expressed by 12 medical members of the Empire Rheumatism Council,[9] and several detailed papers we have printed in the last few weeks show that if deoxycortone with ascorbic acid has any pharmacologically valuable effects they are obtained only irregularly and do not produce objective changes that can be readily measured." "Undoubtedly," they continue, " 'Cortisone' and adrenocorticotropic hormone can remove the symptoms, but the improvement seems to take much longer than the 5 to 15 minutes claimed for deoxycortone." They then mention the further condemnation from Dr. Kendall and Dr. Hench at the National Academy of Sciences held in April and as reported in the *New York Times* of April 25, 1950.

They call attention to the repeated assertions of Kendall and Hench, as has been emphasized herein, that when the effects of cortisone and ACTH were first described, it was pointed out that their importance lay chiefly in the stimulus they would give to research; and this has, of course, been borne out. Deoxycortone and ascorbic acid is one attempt and apparently an unsuccessful one. The *Lancet* mentions pregnenolone, for which definite claims have been made, even though they are less than those made for deoxycortone by some of its supporters. Kendall and Hench, at the same meeting of the National Academy of Sciences held in April, denied that pregnenolone has any action on rheumatoid arthritis or any of the other ills which respond to cortisone.

"The position," says the *Lancet*, "therefore still is that no substances except cortisone and ACTH can yet be held to have substantiated their position in the endocrine treatment of rheumatism."

It may be well to recall at this point that Hans Selye, who has, without doubt, been more familiar with deoxycortone than anyone else, has more recently shown[10] that, in animals, "overdosage with it re produces the experimental equivalent o certain hypertensive, rheumatic, and aller gic diseases of man—in particular, malig nant nephrosclerosis, necrotizing arteriti similar to periarteritis nodosa, cardia nodules resembling Aschoff bodies, join lesions comparable to rheumatic or rheu matoid arthritis, as well as an intense an persistent rise in arterial blood pressure. So it is understandable why the *Lancet*— and British doctors—should be quite per turbed by the exploitation of this dru which was offered as one that might su persede cortisone or ACTH.

* * *

Additional evidence of the realization b the British that everything is not entirel satisfactory is recorded in a recent annota tion[11] in the *Lancet*. It seems that in th last week of March a new film, *Rheuma toid Arthritis: Some Cases Treated wit Deoxycortone and Ascorbic Acid* wa shown to the *press* in London. This film made with two medical men, who hav published at least two articles in the *Lan cet* confirming the results of the Swedish workers, does not (it is stated) set out t show the value of these compounds i therapy but is intended merely to demon strate what happens—or what may happe —when deoxycortone and ascorbic aci are given. The *press*, it may be assumed is to appreciate such hair-splitting differ ence. Of the 7 patients who are included 1 is shown 6 weeks after the start of twice weekly injections, but otherwise the film compares the state before and *half hou* after an injection. "The patients were se lected," 'the accompanying résumé tell us,' quotes the *Lancet*, "only to the exten of their willingness to be photographed subject to this they were consecutiv cases."

In all 7 cases the range and speed o movement was apparently increased; an the "film shows clearly" continues th *Lancet*, "that in a given patient the im provement is not always equal in all joints and that in a given joint some movement may be improved much more than others."

9. "Letters to the Editor," Copeman, W. S. C. and others: Deoxycortone with Ascorbic Acid in Rheumatoid Arthritis, *Lancet*, **1**:830 (April 29 1950. See page 60.

10. Selye, Hans: Production of Hypertension and Hyalinosis by Desoxocortisone, *Brit. M. J.*, **1**: 203 (January 28) 1950.

11. Annotation: Film on Deoxycortone, *Lancet* **1**:675 (April 8) 1950.

It is stated that the makers concede that dosage is not yet settled, and that it is uncertain whether all patients will respond as these 7 were shown to respond and whether the combined treatment will continue to exert a beneficial effect when given for a long time. This concession is admirable. Their object, they say, is simply to record what they have seen. This, they add, is a research film.

This seems fair enough but let it be remembered that the showing was *to the press*. "This being so," continues the *Lancet's* annotation, "the wisdom of releasing it generally among the profession must be seriously questioned—even if, as is proposed, it is used by rheumatologists simply to illustrate lectures." "There is," fears the *Lancet*, "a real risk that this record of immediate effects will gain for the technic closer friends than it has so far been proved to deserve." This leaves the impression that this preview to the press was with the understanding that there were to be no casualties incurred in any mad rush to the telephones to get the story to the "desk" or its British counterpart. Consequently, if this were really so, there would be no chance for the overworked practitioner to learn about the clandestine showing from front page headlines.

In any event the dignified and traditionally conservative *Lancet* seems a bit ruffled that some articles on this superseder of cortisone and ACTH "got by their desk" because summarizing their story of this showing they express the opinion that it is quite certain that it will convert none of the skeptics, who seem still to include a majority of clinicians with wide experience of rheumatism, and particularly those "with experience of cortisone and adrenocorticotropic hormone." "One shot," says the staid and respected *Lancet*, "seems to show diminution in joint swelling half an hour after a single injection; but otherwise there is hardly any objective evidence to change the mind of those who attach weight chiefly to the psychologic effect of this novel method." They also contend that the opportunity to include control observations, which might have met this objection, has unfortunately not been taken.

The *Lancet* should not be too disturbed about the way their columns have been used to extoll the virtues of a combination which now seems to have "flopped." It happens over here much more frequently and they should see the advertising which comes through our mail. It is true that they have been quoted most frequently but, after reading their annotation, their editorial[8] and the article of Currie and Will reprinted elsewhere in this issue, it seems certain that other sources of support will have to be sought. With the trend, to which we have earlier referred, there should be no trouble to find it over here because "headline crashing" is by no means confined to congressmen.

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Eradication of Rabies

In a most enlightening and comprehensive publication from the Lederle Laboratories on the control of rabies, attention is called to the fact that the means of doing just that has been known for three quarters of a century. The successful application of control methods has been demonstrated repeatedly but education, quarantine and mass immunization are the keys to the solution of this problem at the present time just as they have been in the past.

This Lederle communication in its foreword calls attention to the fact that the horrible character of rabies is not sufficiently known to arouse the public to necessary action. "The essence of this difficulty," continues the foreword, "is that rabies never inconveniences the masses, but strikes with relative infrequency, although with fatal results." The victims of rabies are never seen on the street corners, as are those of poliomyelitis. If they were, rabies as a public health problem would soon disappear.

After reviewing the history, epidemiology, immunology, pathology and clinical features of rabies, the development of a new type of rabies vaccine is discussed. This was made possible when the Flury strain of virus became available to research laboratories for further study. Dr. Cox and Dr. Koprowski of the Lederle Research Laboratories then produced a chick embryo vaccine which has definite advantages over previous immunogens. The Flury strain of virus was isolated by Johnson[1] who carried it serially through 138 passages in the brain tissue of day-old chicks, and preliminary tests have shown it to be the strain of choice for use as a living virus immunizing agent. Even at early stages of egg passage, the Flury strain continued to show differences in pathogenicity from others. At higher passage levels, the virulence of the virus decreased so that only 1 out of 10 or more intramuscularly inoculated guinea pigs would show any signs of paralysis and rabbits injected intramuscularly with even the most concentrated virus suspensions showed no signs of paralysis. Inoculated rabbits were found to have practically solid immunity when subsequently challenged, at either 14 or 40 days after immunization, with fixed virus strains. Encouraged by these and many other animal experiments on mice, cotton rats, hamsters, guinea pigs and day-old chicks, the Lederle group began their experiments on dogs to determine the safety of this living virus vaccine and whether it would demonstrate the same high immunizing capacity for dogs as it had shown in guinea pigs and rabbits. Tests for the safety and effectiveness of this vaccine, which has been called Lederle Avianized rabies vaccine, conclusively demonstrated, both in the laboratory and field, that inoculation of dogs does not produce rabies nor has it caused postvaccinal reactions. This living virus has been injected into dogs not only subcutaneously and intramuscularly but directly into the masseter muscles, a highly effective method for inducing rabies in dogs, but no signs of illness have been observed, and tissues from these animals obtained at various intervals after inoculation are devoid of infective power, so there is no danger of dissemination of the virus from vaccinated dogs.

In field trials, over 10,000 dogs of all ages and breeds, some of which had previously received injections of other vaccines, have been vaccinated with the new Avianized vaccine. These animals have been under close observation and no reactions or losses could be attributed to vaccination. The dogs were in various

1. Johnson, H. N.: Rabies in Viral and Rickettsial Infections of Man, Philadelphia, Pennsylvania, J. B. Lippincott, p. 213, 1948.

states of nutrition, and many were in poor condition.

So far these field trials have been conducted in three areas with the approval of the Bureau of Animal Industry of the United States Department of Agriculture. One of these areas was conducted in Georgia under the supervision of Dr. L. E. Starr and Dr. Thomas Sellers of the State of Georgia Department of Health; the second in New York State under the supervision of Dr. Alexander Zeissig of the New York State Department of Health; and a third on Staten Island, New York, under the direct supervision of Doctors Ralph Muckenfuss, Morris Greenberg and Herbert Baum of the New York City Department of Health. About 10,000 dogs have been vaccinated, with highly satisfactory results and with two reactions which did not appear to be due to the vaccine.

Up to this time some have been discouraged because the protective immunity has not been as dependable as was first thought when earlier vaccines were used. Most of these have been killed phenolized or chloroformized rabies vaccines, prepared under optimal conditions. They do possess unquestionable immunogenic properties and are of definite value as immunizing agents, but the immunity produced is relative and not 100 per cent effective. On the other hand, all available data indicate that every dog vaccinated with the new Avianized chick embryo rabies vaccine developed by the Lederle group becomes solidly immune to challenge. It has been shown by Johnson, who developed the Flury strain of virus, that dogs receiving a single 5 cc. injection of killed brain tissue vaccine had a high degree of immunity one month after vaccination. In a group of 105 dogs vaccinated with phenolized vaccine of ovine origin (20 per cent brain tissue), 26, or 25 per cent, died of rabies when challenged one month after vaccination as compared to 66, or 55 per cent, of 120 control dogs; 2 or 4 per cent of 50 dogs vaccinated with chloroformized vaccine of equine origin died of rabies, as compared to 34, or 62 per cent, of 55 control dogs.

In contrast to this, experiments in which dogs were given a single 5 cc. injection of this new Avianized rabies vaccine (thirtieth to eightieth egg passage level) intramuscularly in the hind leg, and challenged by bilateral, intramasseter muscle inoculation with a suspension of dog salivary gland containing virulent street virus, three weeks to one year later, 100 per cent of the vaccinated dogs were protected against rabies, while approximately 70 per cent of the unvaccinated controls died of this disease.

Apparently the development of this new Avianized chick embryo rabies vaccine has met another challenge. With the convincing evidence that it is 100 per cent effective in causing immunity in dogs, it should not be as hard to sell the idea of annual vaccination to the public who without question have become skeptical because we could not assure them that complete protection was obtainable with killed vaccines. Consequently, the medical profession should now put forth a renewed effort to reawaken interest in the prevention of rabies.

The most effective means of doing this is by universal licensing of dogs which should be conditional upon annual vaccination. Then when rabies appears in a community, as it does annually, strict quarantine of all dogs, together with vaccination of all dogs in the area, should be required. We do just that when smallpox appears in a community even though it is a sort of tardy stable-locking gesture. We immunize against tetanus whenever a risk is suspected. Neither disease is more hideous than rabies. The National Research Council and the American Veterinary Medical Association published a comprehensive report in 1946 on the best means of controlling rabies. Certainly the time is long overdue for a concerted effort to have a national program. The suggestion that there should be a coordinated plan of the Bureau of Animal Industry, the United States Fish and Wildlife Service (to include wild animal carriers), the United States Public Health Service and state and municipal health agencies is incontrovertible. A full time veterinarian should be in charge at the state level and the vaccine should be available free for those who cannot pay. It must be 100 per cent effective. The new vaccine should remove all obstacles to a national campaign.

Deoxycortone with Ascorbic Acid in Rheumatoid Arthritis

Sir,—The difference between the excellent results reported in your columns in the treatment of rheumatoid arthritis with deoxycortone acetate and ascorbic acid (Lewin and Wassén 1949, Le Vay and Loxton 1949, Fox 1949, Loxton and Le Vay 1949, Douthwaite 1949, Robertson 1950, Fox 1950, Nashat 1950, Landsberg 1950, Le Vay and Loxton 1950, Hallberg 1950, Spanopoulos 1950, and Morelli and Pusateri 1949) and those obtained by the clinical members of the Empire Rheumatism Council Scientific Advisory Committee and Research Subcommittee (using the same substances and essentially the same technique) has prompted this letter.

The original proponents of this method of treatment claimed that "15 to 30 minutes later" (after the injection) "pain had practically disappeared and the mobility improved as much as the anatomical changes in the joints and muscular atrophy would allow. All the patients reacted in a similar way. In some cases the improvement was astounding. One of the patients was completely crippled by pain and contractures after rheumatoid arthritis for 15 years: after *one* combined injection, she sat up with ease and moved her arms and legs about freely: all her pain had gone. . . . The effect lasted from 2 to 6 hours, occasionally more than 24 hours"—and occasionally "2 or 3 weeks."

Such results are claimed also by the various authors mentioned above, from Poland, Cyprus, Naples, and Bagdad as well as from England. It is noteworthy, however, that such an experienced investigator as Spies (1949) as well as Hart and Starer (1949), Currie and Will (1950), and some of us (Kellgren 1949, Hartfall and Harris 1949, Fletcher et al. 1950, Kersley, Mandel and Jeffrey 1950) have already published results at variance with those described above.

The undersigned, each of whom has had experience in the assessment of "cures" in rheumatoid arthritis, have unanimously found this treatment to be of no significant benefit in rheumatoid arthritis.

The total of cases treated amounts to 172. Of these some limited improvement was noted in 14 cases (subjective only in 11 and objective in 3). Many of us have had the opportunity of treating cases with adrenocorticotrophic hormone and of observing in the U.S.A. the therapeutic effects of 'Cortisone,' and we were convinced immediately of the very great value of these substances. In contrast, when cases are adequately studied under controlled and standardised conditions, treatment with deoxycortone and ascorbic acid produces no more improvement either subjectively or objectively than can be observed to follow other forms of injection treatment—e.g., procaine or even normal saline.

In view of the widespread publicity being given to the use of deoxycortone and ascorbic acid in the treatment of rheumatoid arthritis we have thought it desirable to report our failure to obtain any significant benefit and to record the unanimity with which we are agreed on this.—W. S. C. Copeman, J. J. R. Duthie, E. Fletcher, G. N. Myers, O. Savage, F. Dudley Hart, J. H. Kellgren, Philip Ellman, G. D. Kersley, H. A. Burt, E. G. L. Bywaters and S. J. Hartfall, Letters to the Editor: *Lancet*, 1: 830 (April 29) 1950.